A PROSPECTIVE OBSERVATIONAL STUDY OF RISK INDICATORS ASSOCIATED WITH THE DEVELOPMENT OF THROMBOCYTOPENIA IN A COMMUNITY-BASED ICU/CCU

by

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ABSTRACT

INTRODUCTION: Thrombocytopenia is a common complication in critically ill patients and can present a challenging clinical problem. Its incidence has been reported to range between 13% to 41% and is associated with an increased length of hospital stay and mortality. Information is needed to clarify risk indicators associated with the development of thrombocytopenia in critically ill patients and to improve clinical decision-making when addressing this common problem.

OBJECTIVES:

1. To estimate the incidence of thrombocytopenia in a community based intensive and coronary care unit (ICU/CCU).
2. To compare the incidence of thrombocytopenia in ICU and CCU patients
3. To identify risk indicators associated with the development of thrombocytopenia in ICU/CCU patients using logistic regression modelling.
4. To compare clinical outcomes among patients who did and did not develop thrombocytopenia during their ICU/CCU stay.

DESIGN: A prospective, observational, study.

SETTING: The Intensive/Coronary Care Unit (ICU/CCU) at Lions Gate Hospital (LGH), which is a 350 bed community-based hospital in North Vancouver, British Columbia, Canada.

PATIENTS: The target population for this study included all patients over the age of 18 years who had 2 or more platelet counts recorded, at least 12 hours apart, during an ICU/CCU admission. All patients were included unless they met any of the exclusion criteria, which included an admission platelet count $< 150 \times 10^9$/L, repeat admission to the unit, concurrent involvement in another study, indication of hypersplenism, and particular disease states associated with the development of thrombocytopenia.

METHODS: Data were obtained prospectively during each patient's ICU/CCU stay through daily review of the medical record, patient interviews, and discussion with the medical team. Most responsible diagnoses, clinical outcomes, and any missing data were obtained

retrospectively from the patients' medical charts approximately six weeks after discharge from hospital. Thrombocytopenia was defined as two consecutive platelet counts < 150 x 10^9/L at least 12 hours apart. Descriptive analysis was used to summarize baseline demographic characteristics of the study sample, as well as to select potential variables for logistic regression analysis. Univariate analyses identified variables ($p < 0.25$) potentially associated with thrombocytopenia, which were then subjected to multivariate backward stepwise logistic regression using ($p_{out} > 0.10$ and $p_{in} < 0.05$) to generate two different models. The first model was an admission or baseline model that identified risk indicators independently associated with thrombocytopenia upon admission to the ICU/CCU. The second was a model that included indicators present on admission and those that patients were exposed to in the ICU/CCU.

RESULTS: Of the 362 patients who met the inclusion criteria, 68 (18.8%; 95% CI: 14.8% - 22.8%) developed thrombocytopenia during their ICU/CCU stay. Thrombocytopenia developed more often in patients with an ICU (29.7%; 95% CI: 22.9% - 36.5%) than CCU (8.9%; 95% CI: 4.9% - 12.9%) most responsible diagnosis. Baseline multivariate logistic regression analysis identified eight risk indicators independently associated with the development of thrombocytopenia: sepsis, gastrointestinal diagnosis, GI bleed diagnosis, respiratory non-surgery diagnosis, musculoskeletal/connective tissue diagnosis, age[1], APACHE II Score, and admission platelet count[1]. The ICU/CCU model identified nine risk indicators independently associated with thrombocytopenia: sepsis, gastrointestinal diagnosis, respiratory non-surgery diagnosis, musculoskeletal/connective tissue diagnosis, packed red blood cell (PRBC) transfusion, fresh frozen plasma (FFP) transfusion, Swan-Ganz catheter insertion, acetylsalicylic acid (ASA)[1], and admission platelet count[1]. Exploratory analysis identified bleeding episodes as a possible risk indicator for thrombocytopenia. No medications, including heparin, were found to be associated with increased risk of developing thrombocytopenia following multivariate

[1] Age, ASA, and admission platelet count were negatively associated with the development of thrombocytopenia

logistic regression analysis. Clinicians discontinued heparin in 18% of the patients who developed thrombocytopenia, apparently due to concern regarding HIT. Mean length of ICU/CCU and hospital stays, and mortality were greater among patients who developed thrombocytopenia.

CONCLUSIONS: Thrombocytopenia developed in approximately 19% of patients admitted to a community based ICU/CCU. Indicators associated with an increased risk for thrombocytopenia included markers for severity of illness (e.g. sepsis, APACHE II score, or respiratory non-surgery diagnosis), foreign surfaces (e.g. Swan-Ganz catheters), and, based on an exploratory finding, episodes of bleeding. The identified risk indicators should be considered when treatment decisions are made in critically ill thrombocytopenic patients.

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ACS	Aqueous counting scintillant
AIDS	Acquired immunodeficiency syndrome
ALK	Alkaline Phosphatase
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
APACHE II	Acute Physiology and Chronic Health Evaluation II
APS	Acute Physiology Score
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATIII	Antithrombin III
CCU	Coronary Care Unit
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CK-MB	Creatine kinase MB isoenzyme
CV	Coefficient of variation
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ED	Emergency department
ELISA	Enzyme linked immunosorbant assay
FFP	Fresh frozen plasma
GP	Glycoprotein
HIV	Human immunodeficiency virus
LGH	Lions Gate Hospital

LMWH	Low-molecular-weight heparin
HAT	Heparin-associated thrombocytopenia
HIT	Heparin-induced thrombocytopenia
ICU	Intensive Care Unit
ICU/CCU	Intensive Care Unit/Coronary Care Unit
IgA	Immunoglobin A
IgG	Immunoglobin G
IgM	Immunoglobin M
L	Litres
OR	Odds Ratio
PE	Pulmonary embolism
PF4	Platelet factor 4
PRBC	Packed red blood cells
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SRA	Serotonin release assay
TCPA	Thrombocytopenia
UH	Unfractionated heparin
VWF	Von Willebrand factor

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INTRODUCTION

1.1 PLATELETS AND HEMOSTASIS

Blood coagulation and fibrinolysis result from a complex balance of cellular factors and plasma proteins that maintain the fluidity of blood, while allowing clot formation to occur when needed (Goyette, 1997). One important constituent of the hemostatic system is platelets. Platelets are small anucleate cytoplasmic fragments that arise from the fragmentation of megakaryocytes. They adhere to subendothelial surfaces of damaged blood vessels, aggregate with one another, and amplify the cascade leading to thrombin generation (Goyette, 1997; Ware and Coller, 1995; Handin, 1994; Coller, 1990; Hamilton, 1986). These actions promote normal hemostasis by facilitating platelet plug formation (primary hemostasis) and then reinforcing the plug via thrombin-mediated conversion of fibrinogen to fibrin strands (secondary hemostasis).

One important test of the primary hemostatic system is the platelet count (Handin, 1994). It is an important laboratory value in the diagnosis of bleeding disorders because it reflects the balance between platelet production by bone marrow megakaryocytes and platelet destruction or sequestration (Bessman, 1989). It is useful because it correlates well with the predilection to bleed and is readily available. The normal platelet count is usually in the range of 150 - 450 $\times$ 10^9/L of blood, depending in part on the counting method used (Davis, 1998; Goyette, 1997; Williams *et al.,* 1995; Bithell, 1993; Bessman, 1989; Hamilton, 1986). Normally, two thirds of the circulating platelet pool is present within the intravascular system (blood vessels) while the other third is present (sequestered) within the spleen (Goyette, 1997; Bithell, 1993; Hamilton, 1986). The platelets within these two compartments are freely exchangeable. Platelets have a life span of 7 to 12 days, and the normal rate of turn over is 35 $\times$ 10^9/L/day (Bithell, 1993; Hamilton, 1986).

1.2 DEFINITION AND CAUSES OF THROMBOCYTOPENIA

Thrombocytopenia can be defined as a decrease in the absolute number of circulating platelets below the reference range (150×10^9/L) (Warkentin and Kelton, 2000; Davis, 1998; Bessman, 1989; Handin, 1994; Lind, 1995; Sultan, 1985). It is a clinical sign and not a diagnosis (Warkentin and Kelton, 1994). Patients with thrombocytopenia generally demonstrate a prolonged bleeding time and normal partial thromboplastin and prothrombin time. Thrombocytopenia is clinically important to detect and treat because it is the most common cause of bleeding, and severe thrombocytopenia is often associated with spontaneous bleeding in hospitalized patients (Warkentin and Kelton, 1994). Recently, George *et al* (1998) performed a systematic review of published case reports of drug-induced thrombocytopenia in order to determine drugs that are most likely to cause thrombocytopenia and to provide standardized criteria for reporting drug-induced thrombocytopenia. They assigned a definite or probable causal role for the drug in 247 of 561 (44%) patient case reports. Of the 247 patients described in the case reports, 23 (9%) had experienced major bleeding and 2 (0.8%) died of bleeding.

Generally, when the platelet count is greater than 100×10^9/L, patients are not symptomatic and the bleeding time remains normal (Williams *et al.,* 1995; Bithell, 1993). Patients with platelet counts less than 50×10^9/L bruise more easily and those with platelet counts below 20×10^9/L have an increased incidence of spontaneous bleeding (Davis, 1998; Handin, 1994; Lind, 1995). When bleeding occurs, it is usually mucocutaneous (Warkentin and Kelton, 1994). Clinical signs of small vessel bleeding include petechiae, purpura, and ecchymoses. A more serious hemostatic problem is indicated by mucous membrane bleeding, gingival bleeding, gastrointestinal or urinary bleeding, and epistaxis (Davis, 1998; Hamilton, 1986). Platelet transfusions are given prophylactically or therapeutically to thrombocytopenic patients and to patients undergoing invasive procedures (Kickler, 2000). There is considerable interest in defining the lowest platelet concentration at which bleeding is unlikely, thus minimizing prophylactic platelet transfusions. Researchers have not been able to identify a distinct threshold for increased bleeding risk, but it is thought that the risk of bleeding increases progressively as the platelet count decreases (Kickler, 2000; Warkentin and Kelton, 1994). Despite the lack of a clear threshold, it is

generally considered that patients with a platelet count < 20×10^9/L, in the absence of trauma, surgery, or bleeding require platelet transfusions (Kickler, 2000; Bogdonoff *et al.*, 1990; Warkentin and Kelton, 1994).

The definition of thrombocytopenia used in the clinical and research literature varies widely, depending on the reason for identification of patients with thrombocytopenia. For example, immune thrombocytopenia related to heparin therapy is defined as a single platelet count below the reference range, or a 50% decrease in platelets from baseline (Warkentin *et al.*, 1998). Other authors have used a definition for thrombocytopenia of < 100×10^9/L, as this is when the risk of induced bleeding increases, and some authors have defined thrombocytopenia as < 150×10^9/L because this is usually 2 standard deviations below the mean platelet count determined for normal healthy individuals. However, the risk of clinically significant bleeding is not increased when the platelet count is between 100×10^9/L and 149×10^9/L. Usually, investigators do not justify their choice for the threshold used to define thrombocytopenia. Some investigators classify thrombocytopenia as mild, moderate, or severe (Bonfiglio *et al.*, 1995; Hanes *et al.*, 1997; Baughman *et al.*, 1993), presumably based on a perceived increase in patients' propensity to bleed.

Clinical criteria used to define thrombocytopenia have also included either a single or two consecutive platelet counts below the threshold. Studies analyzing risk factors for the development of thrombocytopenia in critically ill patients (Baughman *et al.*, 1993; Bonfiglio *et al.*, 1995; Hanes *et al.*, 1997; Cawley *et al.*, 1999; Stephen *et al.*, 1999) have used one platelet count below the threshold to define thrombocytopenia, whereas, in a study investigating immune thrombocytopenia due to heparin therapy, the authors required two consecutive platelet counts below the threshold (Warkentin *et al.*, 1995). Perhaps studies that adopt a criterion of two consecutive platelet counts below the threshold are being more rigorous in dealing with intra-patient variability in platelet count, particularly in critically ill patients.

1.2.1 Causes of thrombocytopenia

Thrombocytopenia generally occurs as a result of the following mechanisms: (1) decreased bone marrow production of megakaryocytes (marrow infiltration with tumor, cytotoxic drugs), (2) increased sequestration of circulating platelets by the spleen (splenic hypertrophy from portal hypertension) or dilution of the platelet count by multiple blood transfusions, and (3) decreased platelet survival time due to increased destruction of circulating platelets (nonimmune destruction from sepsis or vasculititis or immune destruction from medication associated antibodies) (Warkentin and Kelton, 1994; Bithell, 1993a).

1.2.1.1 Decreased platelet production

Decreased platelet production can result from a reduction in megakaryocytes in the bone marrow (Warkentin and Kelton, 1994; Bithell, 1993a; Bogdonoff et al., 1990). This can be due to congenital hypoplasia of the megakaryocytes (Fanconi's syndrome, thrombocytopenia with absent radii, intrauterine exposure to drugs, such as thiazides in the newborn, and viral infections, such as rubella), acquired hypoplasia of the megakaryocytes from the action of chemicals, drugs (thiazides, alcohol, diethylstilbestrol), chemotherapy, radiation, or infectious agents, or infiltration of the bone marrow by malignant cells. This generally results in a decreased number of megakaryocytes (Warkentin and Kelton, 1994; Bogdonoff et al., 1990).

Chronic vitamin B_{12} or folic acid deficiencies are seen in some hospitalized patients and are associated with thrombocytopenia (Burstein, 2000; Bogdonoff et al., 1990). The pathophysiologic mechanism is ineffective production, because megakaryocyte numbers are normal or increased in the bone marrow, and platelet survival is normal or slightly shortened. The platelet count usually recovers following administration of the appropriate vitamin. Nitrous oxide administration can result in transient bone marrow dysfunction and thus, thrombocytopenia (Bogdonoff et al., 1990). Mechanically ventilated, critically ill patients are sometimes administered nitrous oxide in order to increase oxygenation of the blood. Although megaloblastic changes are found more commonly in patients exposed to nitrous oxide, these patients are sicker, suggesting that other factors are also involved (Bogdonoff et al., 1990).

Ineffective thrombopoiesis results in decreased circulating platelets, even though the marrow megakaryocytes are normal or in fact elevated in number. This disorder may be due to defective platelet formation, abnormal marrow release of platelets, or destruction of platelets within the bone marrow. In addition, disorders of the control of thrombopoiesis can result in decreased platelet production; however, they are not very common. Decreased platelet production usually occurs with underproduction of other blood cell lines, and is therefore often accompanied by pancytopenia (anemia or granulocytopenia) (Warkentin and Kelton, 2000; Wazny and Ariano, 2000).

1.2.1.2 Altered sequestration and dilution of platelets

Increased platelet sequestration can result in thrombocytopenia due to an abnormal distribution of platelets (Warkentin and Kelton, 2000; Warkentin and Kelton, 1994; Bithell, 1993a). The spleen normally pools approximately one-third of the circulating platelets. Patients with splenomegaly or hypersplenism usually sequester an increased percentage of circulating platelets in the spleen, thus resulting in thrombocytopenia. A massively enlarged spleen can hold > 90% of the total platelet mass and in the absence of abnormally high platelet production, the total body platelet mass and platelet lifespan remains normal, despite low numbers of circulating platelets (Warkentin and Kelton, 2000). Usually, the transit time of platelets through the spleen remains normal (i.e. 10 minutes), but the absolute number of platelets retained within the enlarged spleen is increased. In hypersplenism, the platelet count is usually $50 - 150 \times 10^9$/L, and rarely decreases to $< 20 \times 10^9$/L.

Hypothermia has been reported to result in mild thrombocytopenia (Bogdonoff *et al.*, 1990). Platelet aggregation and activation are the likely mechanisms for the thrombocytopenia. Clinical bleeding is usually not associated with the thrombocytopenia and rewarming usually reverses the platelet count.

Hemodilution can result in decreased numbers of red cells, white cells, and platelets following the administration of blood products, colloids, or crystalloids (Warkentin and Kelton, 2000; Bogdonoff *et al.*, 1990). Several authors have noted that massive transfusion of blood products can lead to dilution of the platelet count (Bucur *et al.*, 2000; Warkentin and Kelton, 1994; Bogdonoff *et al.*, 1990; Reed *et al.*, 1986; Noe *et al.*, 1982; Counts *et al.*, 1979; Murphy and Gardner, 1969), and Riska *et al* (1988) reported that

more than 20 units of whole blood transfused within 24 hours is a potential risk indicator for thrombocytopenia. The decline in platelet count can be attributed to dilution of platelets in the circulation by blood products containing low concentrations of viable platelets (Bogdonoff *et al.*, 1990) or sequestration of platelets by the spleen following blood transfusions (Bareford *et al.*, 1987).

1.2.1.3 Increased destruction of platelets

Destruction of platelets is the most common reason for thrombocytopenia, especially in critically ill patients (Bogdonoff *et al.*, 1990). Thrombocytopenia caused by increased platelet destruction occurs when the rate of platelet destruction exceeds the ability of the bone marrow to produce platelets. Excessive platelet destruction leading to thrombocytopenia can either be non-immune or immue mediated (Warkentin and Kelton, 2000; Handin, 1994; Bogdonoff *et al.*, 1990).

1.2.1.3.1 Non-immune mediated platelet destruction

Non-immune mediated platelet destruction can result from abnormal blood vessels, fibrin thrombi, and intravascular prostheses or surface interactions, all of which can shorten platelet survival (Warkentin *et al.*, 2000; Handin, 1994; Bogdonoff *et al.*, 1990). Some uncommon causes of non-immune mediated platelet destruction include snakebites, transfusion reactions, and obstetric complications, all of which lead to thrombocytopenia through rapid and profound destruction of platelets (Bogdonoff *et al.*, 1990). Burns are also an uncommon cause of non-immune mediated platelet destruction and the degree of decline in the platelet count is generally related with the severity of the burn (Bogdonoff *et al.*, 1990). The decrease in circulating platelets is the result of decreased platelet survival and burn wound sequestration.

There are more common causes of non-immune platelet destruction, especially in critically ill patients. Surface-mediated non-immune platelet destruction can involve abnormal or injured vasculature or tissue, or a foreign body (Warkentin and Kelton, 2000; Bogdonoff *et al.*, 1990). In most of these cases thrombocytopenia results from local platelet destruction, however systemic destruction can also occur as well. Swan-Ganz (pulmonary artery) catheters have been reported to be associated with a non-immune

mediated decline in the platelet count as a result of local or systemic platelet destruction (Bonfiglio *et al.*, 1995; Bogdonoff *et al.*, 1990; Kim *et al.*, 1980; Miller *et al.*, 1984; Layon, 1999; McNulty *et al.*, 1998; Rull *et al.*, 1984). In a prospective study involving 193 critically ill mixed surgical-trauma patients, Cawley *et al* (1999) observed that insertion of invasive central or arterial lines was independently associated with thrombocytopenia. In a retrospective study of 162 medical intensive care unit (ICU) patients, Baughman *et al* (1993) found that pulmonary artery catheter use was associated with thrombocytopenia following univariate analysis, but not after multivariate linear regression analysis. The non-immune mediated decline in the platelet count experienced by some patients following insertion of these catheters is likely the result of local thrombogenesis and hence, platelet destruction (Bogdonoff *et al.*, 1990). In addition, Swan-Ganz catheters are associated with heparin use, as heparin is bonded to their surface and low doses of heparin are continuously infused to keep them patent. It is possible that heparin might contribute to the decline in the platelet count, as described below (Section 1.2.1.3.2).

Abnormalities in platelet survival have been reported in patients with valvular or arterial prostheses and those with abnormal cardiac valves and surfaces (Bogdonoff *et al.*, 1990). However, platelet survival appears to be less of a problem with the prosthetic valves in use today, and thrombocytopenia rarely develops (Wazny and Ariano, 2000; Bogdonoff *et al.*, 1990).

Other foreign surfaces that might be associated with the development of thrombocytopenia include: intra-aortic balloon counterpulsation, dialysis membranes (Bogdonoff *et al.*, 1990), and artificial heart implantation (Wazny and Ariano, 2000). In the case of intra-aortic balloon counterpulsation and dialysis membranes, a decline in the platelet count is the result of platelet aggregation to the foreign surface. Following artificial heart implantation, platelets are damaged by the foreign surface, resulting in a decrease in the platelet count. However, thrombocytopenia is a rare complication in these cases.

Respiratory failure, especially acute respiratory distress syndrome (ARDS), has also been reported to be associated with non-immune mediated platelet destruction (Bogdonoff *et al.*, 1990; Heffner *et al.*, 1987; Schneider *et al.*, 1980; Bone *et al.*, 1976). Animal studies have documented the pulmonary sequestration of platelets in experimental ARDS and Hechtman *et al* (1978) demonstrated pulmonary sequestration of platelets in patients with respiratory failure, but they could not directly relate the

observed thrombocytopenia with the measured platelet loss into the lungs. Patients with respiratory failure or ARDS commonly develop thrombocytopenia, but what remains unclear are the site and mechanism of platelet destruction (Bogdonoff *et al.*, 1990). Interestingly, patients with ARDS frequently display overt evidence of disseminated intravascular coagulation (DIC) (Bogdonoff *et al.*, 1990; Bone *et al.*, 1976).

DIC is characterized by the widespread activation of the coagulation cascade and can cause non-immune platelet destruction (Bogdonoff *et al.*, 1990; Levi and ten Cate, 1999). DIC is an acquired disorder occurring in a wide variety of clinical disorders such as sepsis, trauma (head injury), cancer, or vascular disorders (Levi and ten Cate, 1999). Infectious disease, particularly septicemia, is the most common clinical condition associated with DIC and bacterial infection is most frequently associated with development of this syndrome. Components of the microorganism, including endotoxin (lipopolysaccharide) or exotoxin (staphylococcal α hemolysin) trigger the activation of diffuse coagulation. These components may induce a generalized inflammatory response, which activates the cytokine network. Clinically, the patient presents with decreased platelets and coagulation factors, bleeding, and organ failure. The pathogenesis for DIC is a systemic inflammatory response, mediated by several proinflammatory cytokines (interleukin-6, TNF-α). First, systemic formation of fibrin results from increased generation of thrombin. The increased thrombin generation is mediated mainly by the extrinsic pathway and involves tissue factor (source is not clear, but may be expressed on surface of mononuclear and endothelial cells in response to proinflammatory cytokines) and activated factor VIIa. In addition, endotoxins may trigger the cytokines interleukin-6 and TNF-α, resulting in increased thrombin generation. Next, there is a simultaneous suppression of physiologic anticoagulation mechanisms, including antithrombin III, protein C, and tissue factor-pathway inhibitor. This results in delayed removal of fibrin due to impaired fibrinolysis; the fibrinolytic system is suppressed at the time of maximal activation of coagulation due to an increased plasma level of plasminogen-activator inhibitor type 1 (main inhibitor of the fibrinolytic system). Therefore, in patients with DIC, fibrin formed as a result of thrombin generation is the result of an over active coagulation system, resulting in platelet destruction. The diagnosis of DIC is based on recognition of underlying disease(s) known to be

associated with the condition, a platelet count < 100×10^9/L or a rapid decline in the platelet count, prolongation of clotting times (PT aPTT), presence of fibrin-degradation products, and low plasma levels of plasma clotting inhibitors (AT-III).

Infections are associated with non-immune mediated platelet destruction. Bacterial, viral, fungal, protozoal, and rickettsial infections are associated with thrombocytopenia as a result of intravascular coagulation that causes platelet destruction (George and El-Harake, 1995; Bogdonoff *et al.*, 1990). Most patients with bacteremia become thrombocytopenic, and in some cases, the thrombocytopenia can be severe (George and El-Harake, 1995). DIC is the underlying cause of thrombocytopenia in many bacteremic patients with severe thrombocytopenia, but is not commonly present when the thrombocytopenia is less severe. In most patients, the course of thrombocytopenia parallels the acute infection. In some gram-negative bacterial infections, platelet destruction may occur by platelet aggregation on endotoxin-stimulated monocytes. Another mechanism of thrombocytopenia in patients with endotoxemia is neutrophil activation causing co-sequestration of platelets. It has been suggested that, in gram-positive bacterial infections, exotoxins may directly damage platelets, resulting in thrombocytopenia (George and El-Harake, 1995), and platelets can be directly aggregated by staphylococci and streptococci. In conditions such as septicemia, platelets are usually affected early in the disease course (Bogdonoff *et al.*, 1990), and therefore, thrombocytopenia may be an early warning sign of sepsis. Another mechanism of non-immune mediated platelet destruction is adhesion and aggregation of platelets to endothelium damaged by infectious organisms or their products (e.g. endotoxin).

There are also disorders that are associated with platelet destruction by uncertain mechanisms (Warkentin and Kelton, 2000). One example is thrombotic thrombocytopenic purpura (TTP), which is a fulminant, often lethal disorder that may be initiated by endothelial injury and subsequent release of von Willebrand factor and other procoagulant substances from endothelial cells, resulting in platelet aggregation (Handin, 1994). Thrombocytopenia is an essential feature of the condition and, if absent at presentation of TTP, thrombocytopenia usually develops rapidly (George and El-Harake, 1995). The thrombocytopenia is typically severe (< 20×10^9/L) and is consistent with platelet destruction.

1.2.1.3.2 Immune-mediated platelet destruction

Immune-mediated platelet destruction results from interactions of platelets with antibodies, immune complexes, or complement, resulting in clearance of the coated platelets by mononuclear phagocytes in the spleen or other tissues (Bogdonoff *et al.*, 1990; Handin, 1994). The immunologic thrombocytopenias can be classified based on the pathologic mechanism, the causative agent, or the duration of illness. Uncommon causes of immune-mediated thrombocytopenia include post-transfusion purpura and isoimmune neonatal thrombocytopenia (George *et al.*, 1995; Bogdonoff *et al.*, 1990). The most common causes of immune-mediated thrombocytopenia are viral and bacterial infections, idiopathic thrombocytopenic purpura (ITP), and medications. Patients with immune-mediated thrombocytopenia usually do not have splenomegaly and have an active bone marrow with an increased number of megakaryocytes.

1.2.1.3.2.1 Infection induced immune-mediated platelet destruction

An immune mechanism is likely responsible for the platelet destruction seen during some bacterial and viral infections (Bogdonoff *et al.*, 1990). Some patients with gram-positive or gram-negative septicemia, or viral infections (Wazny and Ariano, 2000) have been reported to have elevated levels of platelet-associated IgG. Possible mechanisms for platelet destruction include non-specific binding of IgG to platelet bound bacterial endotoxins or bacterial or viral fragments, forming immune complexes that subsequently bind to platelet F_c receptors.

Thrombocytopenia can present in patients diagnosed with human immunodeficiency virus (HIV) infection (George *et al.*, 1995). The thrombocytopenia is an isolated abnormality, as the spleen is not enlarged and the marrow contains a normal number of megakaryocytes. Most HIV-infected thrombocytopenic patients have decreased platelet production as a direct effect of the HIV infection on megakaryocytes, and increased platelet destruction is likely a result of immune-mediated platelet injury (George *et al.*, 1995) by IgG antibodies binding to glycoprotein (GP) IIb/IIIa receptors and impairing platelet function.

1.2.1.3.2.2 Autoimmune-mediated platelet destruction

Idiopathic thrombocytopenic purpura (ITP) is an acquired disease of children and adults characterized by a low platelet count, a normal bone marrow, and absence of evidence for other diseases (George *et al.*, 1995). The acute onset of severe thrombocytopenia following recovery from an upper respiratory or viral infection is common in children and accounts for 90% of the pediatric cases of immune-mediated thrombocytopenia (Handin, 1994). This syndrome is known as acute ITP. Acute ITP is rare in adults and accounts for < 10% of cases of immune-mediated thrombocytopenia after puberty. Platelet destruction is caused by immune complexes containing viral antigens, which bind to platelet F_c receptors, or by IgG antibodies produced against viral antigens that cross react with platelets in patients with acute ITP. Most adults present with a slow progressing disease, which may persist for years and is known as chronic ITP (George *et al.*, 1995; Handin, 1994). Isolated thrombocytopenia is the primary abnormality and platelet counts are typically higher than in acute childhood ITP. Patients may present with an abrupt decrease in the platelet count and bleeding, and in general, these patients have a prior history of easy bruising. These patients present with an autoimmune disorder with IgG antibodies directed against target antigens on platelet GP receptors, GP IIb/IIIa and GP Ib/IX. These antibodies function to accelerate platelet clearance by the reticuloendothelial system (phagocytic cells) or bind to epitopes on critical regions of these glycoproteins and impair platelet function (George *et al.*, 1995; Warkentin and Kelton, 2000).

1.2.1.3.2.3 Drug-induced non-immune- and immune-mediated platelet destruction

Many common medications can cause platelet destruction, which can result in the development of thrombocytopenia. Some medications, such as chemotherapeutic agents, are cytotoxic and depress megakaryocyte production. In addition, thiazide diuretics, ethanol, and estrogen have been reported to impair megakaryocytes and thus, decrease platelet production (Handin, 1994; Bogdonoff *et al.*, 1990). Ristocetin, a rarely used antibiotic, causes thrombocytopenia through direct toxic platelet destruction (Bogdonoff *et al.*, 1990). Heparin has been shown in animals (Copley and Robb, 1942; Copley and Robb, 1942a; Fidlar and Jacques, 1948; Quick *et al.*, 1948) and humans (Fidlar and Jacques, 1948; Gollub

and Ulin, 1962; Davey and Lander, 1968; Saffle *et al.*, 1980; Schwartz *et al.*, 1985) to cause a transient non-immune decrease in the platelet count. Heparin is frequently used in critically ill ICU and CCU patients and has been noted by Wazny and Ariano (2000) and Bogdonoff *et al* (1990) to be an important risk factor for the development of thrombocytopenia. Heparin-associated thrombocytopenia (HAT) is thought to be a non-immune mediated process (AbuRahma *et al.,* 1991; Greinacher 1995; Chong 1995; Chong and Castaldi, 1986) associated with a moderate drop in the platelet count within the first 4 days of heparin therapy (Chong 1992; Chong 1995; Greinacher, 1995; Borkowski and Force, 1995). The platelet count seldom drops below 100×10^9/L and often returns to normal levels despite continued heparin administration, while patients usually remain asymptomatic. HAT has been estimated to occur in as many as 10% of all patients administered intravenous heparin (Wazny and Ariano, 2000; Ansell *et al.*, 1980; Greinacher 1995). The mechanism of HAT is thought to be related to the mild platelet pro-aggregating effect of the heparin molecule (Chong, 1992; Chong, 1995; Greinacher, 1995). When heparin is administered, it is possible that it can induce the formation of tiny platelet aggregates and can enhance the platelet-aggregating effect of other platelet-aggregating agents, such as adenosine diphosphate (ADP) (Chong, 1992; Chong, 1995; Greinacher, 1995), epinephrine (Greinacher, 1995), bacteria and/or bacterial products (Chong, 1992; Chong, 1995; Chong and Castaldi, 1986), and immune complexes (Chong, 1992; Chong, 1995; Greinacher, 1995; Chong and Castaldi, 1986). The decline in platelet count could lead to thrombocytopenia in patients who already have a low platelet count. Because heparin is used frequently in critically ill patients who are exposed to many other potential risk indicators for thrombocytopenia, it is not clear whether this pharmacologic effect of heparin is responsible for the observed cases of thrombocytopenia. For example, Bonfiglio *et al* (1995) could not distinguish thrombocytopenia associated with the use of pulmonary artery (Swan-Ganz) catheters from heparin exposure and thus, had to combine pulmonary artery catheter and heparin as a single risk factor. Thus, it is possible that many cases referred to as HAT are actually due to other causes.

Most medications associated with the development of thrombocytopenia elicit an immune response that results in platelet destruction. Patients with medication-induced platelet destruction may have a secondary increase in megakaryocytes, without other marrow abnormalities. In most cases, the

thrombocytopenia is self-limiting, provided the drug is discontinued, and circulating immunoglobulins are the cause of the platelet destruction (George *et al.*, 1995).

Many medications have been reported to result in immunologic destruction of platelets (George *et al.*, 1995; Wazny and Ariano, 2000; Bogdonoff *et al.*, 1990), however, the majority of these have been implicated in less than a dozen cases each. There are five specific medications or medication classes that have been reported to be associated with 60% of all reported cases (Bogdonoff *et al.*, 1990): quinidine, quinine, gold salts, sulfonamides or sulfonamide derivatives, and heparin. In a recent review article, Wazny and Ariano, (2000) provided a comprehensive list of medications that have been reported to be associated with thrombocytopenia; however, many of these were based on a small number of case reports. They noted that, after heparin and antineoplastic agents, medications with the highest frequency and positive evidence of causing platelet destruction were quinidine, quinine, rifampin, and trimethoprim-sulfamethoxazole. Other medications, such as vancomycin, phenytoin, piperacillin, imipenem-cilastatin, and ranitidine, have been reported to be associated with the development of thrombocytopenia in critically ill patients (Bonfiglio *et al.*, 1995; Cawley *et al.*, 1999; Wazny and Ariano, 2000). However, it should be borne in mind that a causal relationship has not been conclusively established, as other factors such as sepsis or Swan-Ganz catheters may have been responsible.

Medication-induced immune-mediated platelet destruction is characterized by the following (Wazny and Ariano, 2000; Warkentin and Kelton, 1994; Bithell, 1993a): an idiosyncratic type of reaction occurring any time after initiation of therapy, presence of normal or increased number of megakaryocytes, reduced platelet survival time, and recovery dependent on the half-life of the causative agent. In addition, the immune-mediated platelet destruction has 3 clinical characteristics. The most common is the occurrence of thrombocytopenia upon re-exposure to the medication. The second characteristic is a pronounced thrombocytopenia developing after long-term medication exposure. This characteristic is rarely reported, and it is not known whether the thrombocytopenia presents as a steady decline in platelet count or a rapid, large decrease. The third characteristic is an acute thrombocytopenia after initial exposure to a medication. There are various immunoglobins implicated in immune-mediated platelet

destruction, the most common being IgG, although IgA and IgM have also been implicated (Warkentin *et al.*, 1998; Arepally *et al.*, 1995; Amiral *et al.*, 1996; Wazny and Ariano, 2000).

The peripheral destruction of platelets may occur by several mechanisms (Bongdonoff *et al.*, 1990; Wazny and Ariano, 2000; Warkentin and Kelton, 2000). First, the medication can bind covalently to membrane glycoproteins and function as a hapten to induce an antibody response. This is the mechanism for most cases of penicillin and penicillin derivative-associated or related immune-mediated thrombocytopenia. Second, quinidine, quinine, and sulfonamides cause platelet destruction by binding noncovalently to a membrane glycoprotein receptor (usually GP IIb/IIIa or GP Ib/IX) to induce conformational changes for which the antibody is specific. The quinidine/quinine-dependent IgG antibody binds to the drug-receptor complex through the F_{ab} portion of the antibody. The F_c portions of the IgG molecules are not involved in binding to platelets, but are available to interact with phagocytic cells of the reticuloendothelial system. Quinidine and quinine can also cause antibody-mediated thrombocytopenia by inducing autoantibodies that bind to platelet membrane glycoproteins without the need for added medication. It is thought that the antibody originally targeted against the medication-glycoprotein complex may directly recognize an antigen on platelets themselves. Third, heparin can cause immune-mediated platelet destruction by binding to a normal protein to form immunolgic complexes to which antibodies bind and form immune complexes. These immune complexes bind to F_c-receptors on platelets, which results in platelet activation.

Heparin-induced thrombocytopenia (HIT) is an immune-mediated thrombocytopenia that is generally characterized by a delayed onset (Chong, 1992; Greinacher, 1995; Ansell *et al.*, 1980; AbuRahma *et al.*, 1991; Borkowski and Force, 1995; Chong, 1995), which usually occurs between 5 and 15 days after commencing heparin therapy (King and Kelton, 1984; Warkentin *et al.*, 1995), and with a maximum incidence around day 10 in patients receiving heparin for the first time (Greinacher, 1995). However, in the case of heparin re-exposure, onset of HIT can occur within the first few days of restarting heparin therapy (Chong, 1995; Greinacher, 1995; Hirsh *et al.*, 1995; King and Kelton, 1984; AbuRahma *et al.*, 1991; Fratantoni *et al.*, 1975). In patients experiencing HIT, the platelet count declines below 100 $\times 10^9$/L, and the median nadir is between 50 to 60 $\times 10^9$/L (Hirsh *et al.*, 1998; Chong, 1995). HIT is

caused by IgG antibodies that recognize an antigen complex of heparin and platelet factor 4 (PF4), an endogenous protein normally present on the surface of endothelial cells or released in small quantities from alpha granules of circulating platelets (Aster, 1995; Lind, 1995; Visentin *et al.*, 1994). After binding with the heparin-PF4 complex, these pathogenic antibodies interact with platelet F_c-receptors eliciting platelet activation (Warkentin *et al.*, 1998; Aster, 1995, Warkentin *et al.*, 1994). HIT was observed to have occurred in 2.7% (95% CI: 1.3% - 5.1%) of postoperative patients who received heparin prophylaxis for deep vein thrombosis for more than 5 days (Warkentin *et al.,* 1995). HIT is different than the other immune thrombocytopenias [idiopathic thrombocytopenic purpura or drug-induced thrombocytopenia (quinidine)] in that bleeding is uncommon despite parenteral anticoagulation and a low platelet count (Chong, 1995; Greinacher, 1995; Warkentin and Kelton, 1991; Borkowski and Force, 1995; Chong, 1988). Patients are at increased risk of developing limb- and life-threatening thromboembolic complications (Chong, 1992; Chong, 1995; Aster, 1995; Ballard, 1999), resulting from a platelet rich thrombus that is distinct from the thrombus for which the heparin therapy was initiated. HIT is diagnosed on the basis of clinical criteria (platelet counts, timing, clinical events) and laboratory tests (^{14}C-serotonin release assay (SRA) and/or enzyme-linked immunosorbant assay (ELISA)). Clinicians usually use the laboratory tests as a supplement to assist in the diagnosis of HIT.

There is no information to date on the incidence of HIT in ICU/CCU patients. HIT is a clinically important drug reaction because heparin is used frequently in these patients and, while those who are suspected of developing HIT usually will not bleed, 20% - 30% of them may develop a serious thrombotic complication. This concern regarding HIT frequently leads clinicians to discontinue heparin when thrombocytopenia develops (Bonfiglio *et al.*, 1995).

1.3 THROMBOCYTOPENIA IN CRITICALLY ILL PATIENTS

Thrombocytopenia is a common complication in critically ill patients and can present a challenging clinical problem when it is severe, putting patients at risk for bleeding, or, in some cases, associated with HIT-induced thrombosis. Critically ill patients are at risk for developing

thrombocytopenia due to the severity of their illness on admission to an intensive care setting, in addition to risk indicators that they may be exposed to during the course of their illness. Most of the research performed to date has involved ICU patients in academic settings, and little work has been performed on the development of thrombocytopenia among patients in coronary care units. While there have been cardiac patients in some of these studies, they usually have comprised a small percentage of the total patient sample (Baughman *et al.*, 1993; Bonfiglio *et al.*, 1995). Many community hospitals, such as the one that was the site in the present study, Lions Gate Hospital (LGH), North Vancouver, B.C., have a combined ICU/CCU and, to date, there has been no investigation of thrombocytopenia in an ICU/CCU setting. Thus, to identify potential risk indicators associated with the development of thrombocytopenia in such facilities, it is important to review the literature with respect to both ICU and coronary care patients.

1.3.1 Studies investigating the development of thrombocytopenia in ICU patients

At present, there are 5 published studies (Baughman *et al.*, 1993; Bonfiglio *et al.*, 1995; Hanes *et al.*, 1997; Cawley *et al.*, 1999; Stephen *et al.*, 1999) assessing the incidence and risk indicators associated with thrombocytopenia in this population, and they are summarized in Table 1.

Baughman *et al* (1993) performed a retrospective chart review of 162 medical ICU patients, admitted over 3 separate months during 1 academic year, to determine the incidence of thrombocytopenia and to identify risk factors apparently associated with thrombocytopenia. The authors defined mild and severe thrombocytopenia as platelet counts less than 100×10^9/L and 50×10^9/L, respectively. They found that 38 of 162 (23%) patients had platelet counts less than 100×10^9/L at least once during their ICU stay, and 17 of 162 (10%) patients had platelet counts less than 50×10^9/L during their ICU stay. Following stepwise multivariate linear regression modelling, the authors identified a number of independent risk factors for severe thrombocytopenia. These included: sepsis, antineoplastic chemotherapy, elevated creatinine level and elevated bilirubin level. The authors also stated that thrombocytopenia was associated with longer ICU stays and increased hospital days, and the in-hospital mortality was higher for those patients who developed thrombocytopenia in the ICU compared to those

TABLE 1

STUDIES INVESTIGATING THE INCIDENCE AND RISK FACTORS* ASSOCIATED WITH THE DEVELOPMENT OF THROMBOCYTOPENIA IN CRITICALLY ILL PATIENTS

Reference	Study Design	Definition of Thrombocytopenia	Frequency of Thrombocytopenia	Risk Factors
Baughman *et al* (1993)	• Retrospective • Over 3 separate months • 162 patients • medical ICU • linear regression	• mild < 100×10^9/L • severe < 50×10^9/L	• mild: 38/162 (23%) • severe: 17/162 (10%)	• sepsis • antineoplastic chemotherapy • elevated creatinine level • elevated bilirubin level
Bonfiglio *et al* (1995)	• retrospective • 18 months consecutive admissions screened • patients in ICU at least 72 hours • 314 patients • mixed medical/ surgical ICU • linear regression	• < 200×10^9/L • simple < 200×10^9/L • significant (moderate) < 100×10^9/L • severe < 20×10^9/L	• overall 69% < 200×10^9/L • simple: 41.8% • significant: 25.2% • severe: 2.0%	• baseline platelet count • hemodynamic stability • inotropic agents • length of ICU stay • length of H_2-antagonist treatment • liver function abnormalities
Stephen *et al* (1999)	• prospective • continuous admissions for 6 months • 147 surgical ICU patients • logistic regression	• < 100×10^9/L	• 52/147 (35%)	• sepsis • episodes of bleeding or transfusions • APACHE II score of > 15

* While the present study used the term risk indicators for independent variables (see Section 2.1.10), the studies referred to in Table 1 used the term risk factors for independent variables.

TABLE 1 CONTINUED

STUDIES INVESTIGATING THE INCIDENCE AND RISK FACTORS* ASSOCIATED WITH THE DEVELOPMENT OF THROMBOCYTOPENIA IN CRITICALLY ILL PATIENTS

Reference	Study Design	Definition of Thrombocytopenia	Frequency of Thrombocytopenia	Risk Factors
Hanes *et al* (1997)	• prospective • observational • patients followed for up to 14 days • patients in ICU at least 48 hours • 63 patients • trauma ICU • logistic regression	• significant < 100 × 10^9/L • moderate < 50 × 10^9/L • severe < 20 × 10^9/L	• significant: 26/63 (41%) • moderate: 2/63 (3.2%) • severe: 0	• age • higher trauma scores • non-head injuries
Cawley *et al* (1999)	• retrospective • during a 3 month period • patients in ICU at least 24 hours • 193 patients • surgical-trauma ICU • linear regression	• < 100 × 10^9/L	• 25/193 (13%)	• central or arterial line

* While the present study used the term risk indicators for independent variables (see Section 2.1.10), the studies referred to in Table 1 used the term risk factors for independent variables.

who did not. It is not possible to determine whether the longer ICU and hospital stays were causally related to thrombocytopenia.

In another study (Bonfiglio *et al.,* 1995), a retrospective chart review was performed to estimate the incidence and severity of thrombocytopenia in 314 patients in a mixed medical-surgical ICU, and to examine risk factors that may have been related to the development of thrombocytopenia. Thrombocytopenia was defined categorically as: simple thrombocytopenia (platelet count $< 200 \times 10^9$/L), significant thrombocytopenia (platelet count $< 100 \times 10^9$/L), and severe thrombocytopenia (platelet count $< 50 \times 10^9$/L). They also calculated the percentage change of each patient's platelet count from baseline (admission) to minimum platelet count. The researchers developed a stepwise linear regression model to examine the independent risk factors for thrombocytopenia. Independent variables, established *a priori*, were analysed using stepwise regression to determine whether they explained a significant proportion of the variance in platelet count. The authors reported that 69% of patients experienced a platelet count $< 200 \times 10^9$/L. The frequency of thrombocytopenia among the three designated categories was 41.8% for simple thrombocytopenia, 25.2% for significant thrombocytopenia, and 2.0% for severe thrombocytopenia. Risk factors reported to be associated with the development of thrombocytopenia following multivariate stepwise linear regression analysis included: baseline platelet count, hemodynamic instability (defined as pulmonary artery [Swan-Ganz] catheter/heparin and a vasoconstrictor), use of inotropic agents, length of ICU stay, length of H_2-antagonist treatment, and liver function abnormalities. However, it is difficult to interpret the contribution of these risk factors, as it is not clear what dependent variable the authors used in the linear regression analysis. Following stepwise linear regression analysis, 57% of the variance in platelet count could be attributed to factors identified in the analysis. The most important factor was baseline platelet count, which reportedly accounted for 43% of the variance (although the dependent variable was not clearly defined).

In a recent prospective, observational study (Hanes *et al.,* 1997), 63 patients in a university hospital ICU were observed in order to determine the incidence and risk factors associated with the development of thrombocytopenia. The authors categorized thrombocytopenia as follows: significant thrombocytopenia was defined as a platelet count less than 100×10^9/L, moderate thrombocytopenia was

a platelet count less than 50×10^9/L, and severe thrombocytopenia was a platelet count less than 20×10^9/L. They used univariate analysis and then forward stepwise multiple logistic regression to identify risk factors associated with thrombocytopenia. Twenty-six of 63 (41%) trauma patients were reported to develop significant thrombocytopenia, whereas only 2 (3.2%) patients developed moderate thrombocytopenia, and no patients developed severe thrombocytopenia. The authors noted that age, higher trauma scores, and nonhead injuries were independently associated with the development of thrombocytopenia following multivariate logistic regression analysis. They also reported that duration of ICU stay was significantly associated with the development of thrombocytopenia. However, duration of ICU stay is an outcome that is only known *post hoc* and thus, its use as a risk factor appears inappropriate.

Recently, Cawley *et al* (1999) conducted a retrospective chart review, over a 3-month period, of 193 surgical-trauma ICU (SICU) patients to determine the frequency of, and risk factors associated with, thrombocytopenia, and the association of acquired thrombocytopenia with length of SICU stay and mortality. Patients were determined to have developed thrombocytopenia if their platelet count declined to less than 100×10^9/L 24 hours or more after admission. The researchers selected a list of potential risk factors *a priori* and performed stepwise multiple linear regression to determine which independent risk factors were associated with the development of thrombocytopenia. Thrombocytopenia was reported in 25 (13%) patients, and the following risk factors were found to be associated with thrombocytopenia based on univariate analysis: non-surgical diagnosis, sepsis, central or arterial line, and administration of phenytoin, piperacillin, imipenem-cilastatin, and vancomycin. In addition, the authors reported that acute respiratory distress syndrome and respiratory failure demonstrated a trend toward an association with thrombocytopenia, but statistical significance was not observed, possibly, because of the small number of patients in these categories. Following multiple linear regression analysis, the authors concluded that only the presence of a central or arterial line was associated with the development of thrombocytopenia. This was likely due in part to the relatively small number of observed cases of thrombocytopenia. They also noted that thrombocytopenic patients had a longer SICU stay and greater mortality.

Recently, Stephan *et al* (1999) prospectively studied 147 consecutive patients admitted to a surgical ICU during a 6-month period, until discharge from the ICU or death, in order to assess the incidence of thrombocytopenia. In addition, they investigated the factors associated with thrombocytopenia, the outcomes among thrombocytopenic patients, and the possible mechanisms involved in the development of thrombocytopenia. The authors defined thrombocytopenia as a single platelet count $< 100 \times 10^9$/L occurring at least once during the ICU stay. They used univariate analysis, with a p-value ≤ 0.05 as the criterion, for selecting variables to be included in stepwise multivariate logistic regression analysis. Fifty-two (35%) of 147 patients developed thrombocytopenia. Following stepwise logistic regression analysis, sepsis, episodes of bleeding or transfusions, and an APACHE II score of > 15 were independent risk factors associated with the development of thrombocytopenia. They reported that the ICU mortality was higher in thrombocytopenic patients (38%) than in non-thrombocytopenic patients (20%) ($p = 0.02$), and the development of thrombocytopenia was associated with an increased ICU stay and a longer hospital stay. The authors stated that thrombocytopenia probably reflected the severity and course of an underlying pathologic condition.

1.3.1.1 Limitations of the studies performed to date

It is apparent from the 5 studies discussed above that thrombocytopenia occurs commonly in critically ill patients, though all studies performed to date have some limitations. First, the findings of Baughman *et al* (1993), Bonfiglio *et al* (1995), and Cawley *et al* (1999) are affected by the retrospective nature of the studies. In general, retrospective studies are limited by information obtained solely from patients' medical charts, and this information can be inaccurate when compared to the same information obtained prospectively, because data may not be recorded accurately or may be missing (Kraemer *et al.*, 1997). Second, four of the studies (Baughman *et al.*, 1993; Hanes *et al.*, 1997; Cawley *et al.*, 1999; Stephen *et al.*, 1999) involved small numbers of patients, which may have reduced the power to detect specific risk factors as being associated with the development of thrombocytopenia. Third, not all suspected risk factors associated with thrombocytopenia in critically ill ICU patients were included in the analyses (Baughman *et al.*, 1993; Hanes *et al.*, 1997; Cawley *et al.*, 1999), suggesting that some missing

risk factors may have accounted for part of the variability in the observed development of thrombocytopenia. Fourth, the studies published to date all lack clarity in the statistical modelling process. The development of thrombocytopenia is usually viewed as a binary outcome, however, only two studies (Hanes *et al.*, 1997; Stephen *et al.*, 1999) used logistic regression analysis to identify independent risk factors associated with the development of thrombocytopenia. The other studies used linear regression analysis, and only Bonfiglio *et al* (1995) reported using a percentage change in the platelet count as indicating the frequency of thrombocytopenia. Fifth, the 5 published studies were conducted in a variety of different critical care settings, and none of these involved patients admitted to a community-based ICU/CCU. Finally, no uniform criteria were used in defining thrombocytopenia in the 5 published studies. An understanding of the limitations of these prior studies has aided in the development of a well designed, prospective, observational study in a community based setting involving both critically ill intensive and coronary care patients.

1.3.2 Studies investigating the development of thrombocytopenia in coronary care settings

The information on the incidence of or risk indicators associated with thrombocytopenia in critically ill cardiac patients that is available has been derived from *post hoc* evaluations of large cardiac clinical trials. However, data suggest that thrombocytopenia can develop during an acute coronary syndrome (acute myocardial infarction and unstable angina) and is associated with adverse outcomes (McClure *et al.*, 1999). McClure *et al* (1999) analyzed data from 9217 cardiac patients enrolled in "the platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) study" to estimate the incidence of thrombocytopenia in placebo- and eptifibatide-treated arms. They reported an overall incidence of thrombocytopenia of 7% and, based on their sample size, the 95% confidence interval (CI) can be calculated to be 6.5% to 7.5%. The definition of thrombocytopenia used by the authors was a nadir platelet count $< 100 \times 10^9$/L, or a decrease of $> 50\%$ from baseline. Patients who developed thrombocytopenia were older, non-white, weighed less, and had more cardiac risk factors (diabetes mellitus, previous myocardial infarction, previous angioplasty). In addition, the investigators performed a multivariate regression analysis in an attempt to identify risk factors and assess

their independent association with thrombocytopenia. Variables associated with the highest risk for the development of thrombocytopenia included coronary artery bypass graft (odds ratio 12.2; 95% CI: 9.1 to 16.2), moderate (i.e. patients requiring blood transfusion, but not hemodynamically compromised that required an intervention) to severe bleeds (i.e. in patients with intracranial bleeding or a bleeding event that caused hemodynamic compromise requiring intervention) (odds ratio 2.4; 95% CI: 1.9 to 3.2), and treatment involving an intra-aortic balloon pump (odds ratio 2.2; 95% CI: 1.5 to 3.2). Other variables independently associated with thrombocytopenia identified by the multivariate regression model were: female sex, history of percutaneous transluminal coronary angioplasty, increasing age, and baseline platelet count. Use of heparin was not associated with the development of thrombocytopenia when evaluated as a dichotomous or continuous variable. Likewise, antiplatelet therapies such as, acetylsalicylic acid, ticlopidine, abciximab, thrombolytics, and eptifibatide were not associated with an increased risk of developing thrombocytopenia.

In a study of patients experiencing acute myocardial infarction, Harrington *et al* (1994) observed that thrombocytopenia was associated with increases in in-hospital mortality, bleeding, and total hospital stay. The authors combined and analyzed data from 874 patients involved in phases 2, 3, and 5 of the Thrombolysis and angioplasty in myocardial infarction (TAMI) trial and a urokinase trial to examine the incidence and clinical implications of thrombocytopenia that occurs after administration of thrombolytic therapy for acute myocardial infarction (AMI). The researchers reported that thrombocytopenia occurred in 16.4% of patients and, based on their study sample, the 95% CI can be calculated to be 13.9% to 18.9%. Thrombocytopenia was defined by either a nadir platelet count $< 100 \times 10^9$/L or a decrease of > 50% from baseline. The researchers did not investigate risk indicators for the development of thrombocytopenia, but noted that patients who developed thrombocytopenia had a lower median acute ejection fraction ($p \leq 0.0001$) and a higher likelihood of three-vessel coronary artery disease ($p \leq 0.0001$) than patients without thrombocytopenia. In addition, patients with thrombocytopenia had a higher in-hospital mortality, length of CCU stay, and length of hospital stay ($p \leq 0.0001$); a higher incidence of congestive heart failure (CHF), recurrent ischemia, and complete heart block; and were more likely to have undergone bypass surgery, balloon pump insertion, and endotracheal intubation than patients

without thrombocytopenia. Lastly, patients who developed thrombocytopenia experienced more blood loss than patients who did not develop thrombocytopenia. Blood loss was quantified by a bleeding index intended to estimate the total number of units of blood lost: units of packed red blood cells (PRBC) transfused plus the change in hematocrit divided by 3.

While these *post hoc* analyses have provided information on the incidence of and risk factors for thrombocytopenia from a substantial number of patients, further research is warranted to determine the extent to which these findings from clinical trials can be generalized to the CCU population.

1.4 LOGISTIC REGRESSION ANALYSIS

1.4.1 Logistic regression

Regression methods are used to describe the relation between a dependent (response) variable and one or more independent (explanatory) variables. The goal of any regression analysis is to build the most reasonable and parsimonious model that remains logical from a clinical point of view (Hosmer and Lemeshow, 1989). The most common example of regression analysis is linear regression modelling, in which the dependent variable is assumed to be continuous. However, when researchers are concerned with a dichotomous dependent variable, logistic regression modelling becomes the standard method of analysis. Logistic regression is based on the principle of regressing a dichotomous dependent variable on a set of independent covariates (risk indicators) (Hosmer and Lemeshow, 1989). The goal of logistic regression analysis in this study is to achieve a predictive mathematical model that describes the relation between thrombocytopenia and a set of independent variables.

Construction of the regression model is achieved through a model-building approach. The process of building a logistic regression model involves: coding of the independent variables; univariate analysis to select variables for multivariate analysis; checking for collinearity among the independent variables selected as candidates following univariate analysis; ascertaining that each of the continuous variables is in the correct scale (check the assumption of linearity in the logit); multivariate analysis to fit a model; checking for interactions among the independent variables in the model; assessing the fit of the

model (the model contains those variables that should be in the model and variables have been entered in the correct functional form); and regression diagnostics to examine the impact of individual subjects in the model.

A regression estimate is used to estimate the probability for each patient (case) to develop the dichotomous outcome. If the probability of the outcome is P, then $P/(1 - P)$ is the odds of the outcome occurring and $\log_e [P/(1 - P)]$ is referred to as the log odds of the outcome occurring. This can be expressed in a linear model as follows:

$$\log_e (P/1 - P) = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$$

The log odds is also called the logit of P (Hosmer and Lemeshow, 1989). It is the natural logarithm of the ratio of two probabilities. The logit acts as a "link" function linking the predicted probabilities to a linear combination of the independent variables where:

β_0 is the estimated intercept coefficient. It is the log odds of the dichotomous outcome variable in the reference group when all the independent variables are 0. Since 0 is outside the clinically meaningful range for some independent variables, for example platelet count or hemoglobin concentration, this coefficient has no clinical interpretation, but is required in the model.

β_1 to β_k are the estimated coefficients of the independent variables. They represent the increase in the log odds that the dichotomous outcome will develop per unit increase in β_k, given that all other independent variables remain constant. In other words, it is the effect of β_k on the outcome, adjusted for all other independent variables. X_1 to X_k are the independent variables.

Logistic regression is used to identify the effect of individual variables and give an estimate of the odds ratio for the individual effect. The odds ratio is defined as the odds in favour of an outcome among individuals exposed to a risk indicator divided by the odds of the event among individuals unexposed to the risk indicator. Interestingly, the odds ratio is a close approximation of the relative risk for rare diseases or outcomes. The coefficients in the logistic regression model represent the change in the logit

of one unit in the independent variable. Interpretation of the coefficient depends on being able to place meaning on the difference between two logits. For example, when the independent variable is dichotomous, the coefficient is the log odds ratio, β (the value of the coefficient). When a logistic regression model contains a continuous independent variable, interpretation of the estimated coefficient depends on how the variable is entered into the model and the specific units of the variable. Assuming that the logit is linear in the continuous variable (X), the slope coefficient, β, represents the change in the log odds for an increase of 1 unit in X. In many cases, an increase of 1 unit will not be biologically or clinically meaningful. Therefore, a change of 10, 25, or 50 units might be considered more useful. The values of the regression coefficients are calculated as the best mathematical fit for a specified model.

Logistic regression is increasingly being used in clinical research, but is often inaccurately and/or ineffectively applied (Concato *et al.*, 1993). Methodologic violations and omissions of detail are often apparent in published results of studies that have used this technique (Concato *et al.*, 1993). These include: overfitting of data (Harrell *et al.*, 1996; Harrell *et al.*, 1985); no tests of conformity of variables to a linear fit; no tests or reporting of tests for interactions between the independent variables; unspecified coding or selection of independent variables; lack of reporting or no tests for collinearity among variables; no tests or reporting of influential observations (i.e. regression diagnostics); and not validating the model generated in the study. These problems make the reporting of results potentially inaccurate, misleading, or extremely difficult to interpret. For example, overfitting of data can result in identification of unstable risk indicators and inappropriate p-values. More importantly, if the model is badly overfitted, it may actually have negative (worse than random) discrimination on a new data set (Harrell *et al.*, 1996). While it is desirable to use a randomized, placebo-controlled study design in clinical research, many clinical problems are not amendable to such a design. This is the case with observational studies, which are frequently used to identify potential risk indicators associated with the outcome being studied, and also to generate models that can be used to predict future events.

1.5 OBJECTIVES OF THE PRESENT STUDY

The overall purpose of this research was to investigate thrombocytopenia and its outcomes in critically ill patients. This research was conducted at a community-based ICU/CCU, and the objectives were:

1. to estimate the incidence of thrombocytopenia in a community based intensive and coronary care unit (ICU/CCU).
2. to compare the incidence of thrombocytopenia in ICU and CCU patients.
3. to identify risk indicators associated with the development of thrombocytopenia in ICU/CCU patients using logistic regression modelling.
4. to compare clinical outcomes among patients who did and did not develop thrombocytopenia during their ICU/CCU stay.

METHODS

2.1 POTENTIAL RISK INDICATORS FOR THROMBOCYTOPENIA

2.1.1 Study design

This was a prospective, observational, study. A database of patient characteristics relating to risk indicators for thrombocytopenia was maintained for each patient meeting entry criteria. Risk indicators identified *a priori*, based on published information, were analyzed using multivariate logistic regression.

2.1.2 Study setting

This study was carried out in the Lions Gate Hospital (LGH) Intensive/Coronary Care Unit (ICU/CCU). LGH is a 350 bed community-based hospital located in North Vancouver, British Columbia with an 11 bed ICU/CCU (6 ICU beds and 5 CCU beds) that admits all patients requiring mechanical ventilation in the hospital, as well as any patients considered to be unstable on a hemodynamic or respiratory basis, to the extent that critical care monitoring is warranted. Approximately 975 patients are admitted to the ICU/CCU at LGH each year.

2.1.3 Patient selection

The target population for this study included all patients over the age of 18 years admitted to the LGH ICU/CCU during the period of June 11, 1997 to June 11, 1998 who had 2 or more platelet counts recorded, at least 12 hours apart, during ICU/CCU admission. All patients were included unless they met any of the exclusion criteria:

2.1.3.1 Exclusion criteria

1. A platelet count less than 150×10^9/L upon admission to the unit
2. Repeat admission to the unit
3. Concomitant participation in another study

4. Hereditary or congenital thrombocytopenia
5. Evidence of hypersplenism
6. Presence of mechanical heart valve
7. Disseminated intravascular coagulation (DIC)
8. Idiopathic thrombocytopenic purpura (ITP)
9. Thrombotic thrombocytopenic purpura (TTP).

The last five exclusion criteria refer to disease states that are known to be associated with thrombocytopenia. However, patients who developed DIC, ITP, or TTP during their stay in the ICU/CCU were to be included in the study. Patients discharged from the ICU/CCU to the ward who were then readmitted to the ICU/CCU within 48 hours of their discharge continued to have their data collected and recorded as though they had not left the ICU/CCU. All *a priori* risk indicators (laboratory values, medications, and procedures) that occurred on the ward were recorded. Patients discharged from the ICU/CCU to the ward and who were then readmitted to the ICU/CCU after 48 hours were considered as re-admissions and had only their first admission data entered into the study.

2.1.4 Ethical approval

The study protocol was approved by the Lions Gate Hospital Research Committee and the Clinical Screening Committee for Research and other studies involving Human subjects at UBC. The Certificates of Approval are attached (Appendices 1 and 2). Since the methods employed did not affect patient care, no informed consent was required from the patients involved in this study.

2.1.5 Sample size for risk indicators associated with the development of thrombocytopenia

The intention of this study was to utilize multivariate logistic regression in order to identify independent risk indicators associated with the development of thrombocytopenia in a community-based ICU/CCU, and to develop a model that could be validated from data obtained from a sample of patients from the same unit. Based on an expected 20 to 30% incidence of thrombocytopenia, as identified in

previous studies in critically ill patients (Bonfiglio *et al.*, 1995; Baughman *et al.*, 1993; Cawley *et al.*, 1999; Stephan *et al.*, 1999), it was estimated that approximately 400 patients would be required for this study (Table 2). The data generated in Table 2 indicate that, based on an expected incidence of thrombocytopenia of 20 to 30% and an estimated target sample of 400 patients, the 95% confidence interval (CI) would be between ± 3 - 5%.

2.1.6 Data collection

Data collection for this study included patients admitted to the ICU/CCU between June 11, 1997 and June 11, 1998. Clinical data were collected prospectively on all study patients daily using a specifically prepared data collection form (Appendix 3). Specific definitions for each variable or group of variables were developed *a priori* for use in categorizing patient data. Data were collected from information routinely recorded during the course of patient care and from specimens drawn as part of usual therapeutic intervention or routine care. Eligible patients were followed prospectively during their stay in the ICU/CCU until discharge or death. Patients who were initially admitted to the Emergency Department (ED) had their data collected from the time they were admitted to the ED until they were discharged from the ICU/CCU or died in the ICU/CCU. Information unattainable during daily data collection, for example, total duration of hospital stay, was collected retrospectively approximately six to eight weeks after discharge from the ICU/CCU. This was accomplished by reviewing the patient's chart in Medical Records. All medical charts were complete so that there were no missing data. All data were recorded in a manner that ensured confidentiality.

2.1.6.1 Data management

All completed data collection forms were coded and entered into a relational database in Microsoft Access® 7.0 by the author to ensure quality and consistency of coding and data entry. Data were then reviewed and verified in Access® 7.0. All entries that the author found ambiguous or problematic were queried and then re-checked. Data were imported into Excel® 4.0 spreadsheet format and then transferred to SPSS® 9.0 for analysis.

TABLE 2

SAMPLE SIZE ESTIMATION BASED ON THE PROPORTION OF PATIENTS WHO DEVELOPED THROMBOCYTOPENIA IN PREVIOUS STUDIES INVOLVING CRITICALLY ILL PATIENTS *

Estimated Incidence of Thrombocytopenia	95% Confidence Interval ± 1%	95% Confidence Interval ± 2%	95% Confidence Interval ± 3%	95% Confidence Interval ± 5%	95% Confidence Interval ± 10%
10%	3457	864	384	138	NR
15%	NR	1225	544	196	49
20%	NR	NR	682	246	62
25%	NR	NR	800	288	72
30%	NR	NR	896	373	81

NR: Not Relevant

* The table summarizes sample sizes required to estimate the incidence of thrombocytopenia in critically ill patients with specified confidence intervals. Calculations were based on a two-sided alpha of 0.05 (95% confidence interval). The following equation is used to estimate the sample size when the estimated proportions, p and q are of sufficient magnitude to use the normal approximation:

$$N = \frac{Z^2_{\alpha}\, p\, q}{\delta^2}$$

where:

N: sample size

Z: two tailed Z value related to an alpha of 1.96

α: the probability of a false positive error; set at 0.05

p: the estimated proportion of thrombocytopenia

$q = 1 - p$

δ: the width of the confidence interval or the maximum amount of error one will tolerate.

2.1.7 Definition of thrombocytopenia

The primary endpoint of the study was the development of thrombocytopenia at any time during a patient's stay in the ICU/CCU. In keeping with definitions recognized clinically, thrombocytopenia was defined as two or more consecutive platelet counts (more than 12 hours apart) below 150×10^9/L (the lower limit of normal recognized by the laboratory at LGH) (Warkentin and Kelton, 2000; Davis, 1998; Bessman, 1989; Handin, 1994; Lind, 1995; Sultan, 1985). The admission platelet count and time to occurrence of thrombocytopenia from admission to the unit was recorded.

2.1.8 Determination of the platelet count

Baseline and daily platelet counts, when available, were recorded, including all platelet counts determined for patients in the ED immediately prior to admission to the ICU/CCU. Whole blood was collected on EDTA for platelet counts. Samples were routinely analyzed within two hours of collection.

Platelet counts were obtained with an electronic (impedance) counter, the Coulter Counter S Plus Model STKR. This model is capable of accepting and mixing up to 144 patient samples at one time for identification, aspiration, and sample analysis (Brown, 1993). The method of counting platelets is based on the Coulter principle. In short, a suspension of blood cells is passed through a small opening (orifice) simultaneously with an electric current (Goyette, 1997). Individual blood cells passing through the orifice produce an impedance change in the orifice as determined by the size of the cell. Counts are made of the individual cells and a cell size distribution is provided (Bessman, 1989; Goyette, 1997). For platelets, the diameter of the aperature is set sufficiently small so that the majority of the platelets will pass through the opening one at a time. A drop in the conductivity as each cell pass through the small aperature is used to count the number of platelets. The instrument can size cells and discriminate between different cell populations on the basis of their volume. The decrease in the electrical flow is proportional to the volume of the cell. Platelets are recognized and counted as particles in the 2 to 20 fL range. In the analyzer unit, a graph is then plotted of the size distribution of the platelets between 2 and 20 fL. The data are then extrapolated to make a smooth curve and it is from this smooth curve that the platelet count is determined. For example, normal platelets, when graphed according to size and number, are log-normally distributed

and generate a log-normal curve. A graph is made of the size distribution of the platelets between 2 and 20 fL, and this graph represents a plot of the actual count between 0 and 20 fL (Threatte, 1993). If the platelet count has a log-normal distribution, the analyzer chooses the peak of the curve and the lowest points on either side of the peak. The two low points are then used to fit the platelet data to a log-normal curve. The fitted curve is plotted from 0 to 70 fL over the original curve and all platelets contained within this curve are counted and reported as the platelet count.

The intra-day coefficient of variation for normal platelet counts varies from 2 to 4 percent for automated counters to 11 percent or more for manual counters, such as phase microscopy (Hamilton, 1986; Williams, 1995). The reference range for a normal platelet count has been established for a number of years at LGH (Dr. Wolber M.D., personal communication, 1998). It is based on a clinically agreed normal range (reference laboratory mean ± 2 standard deviations (SD)). Daily quality controls (internal control) are performed on the Coulter Counter. These consist of a Coulter whole blood reagent control with established normal values for all cell components run once a day, as well as a patient normal whole blood measured four times per day. These should have a coefficient of variation within 10%. An external control provided by the College of American Pathologists is also performed at regular intervals.

An internal control was performed in order to estimate the intra- and inter-day platelet count variability. This determination had to be done with a different sample each day due to the degradation of platelets after 8 to 12 hours. To estimate intra-day variability of the assay, blood samples from 6 patients were each split into 4 aliquots and platelet counts were done using each aliquot. The intra-day coefficient of variation (CV) for each patient's sample was determined and used to calculate the mean CV for the group of 6 patients. To estimate the inter-day variability of the assay, daily blood samples for 6 days were obtained and analyzed from 9 different non-thrombocytopenic patients. The inter-day CV was calculated for each of the 9 patients and the mean of the 9 patients' CV was used to estimate the inter-day variability in platelet count.

2.1.9 Demographic and patient characteristics

Initial admission evaluations included the age, weight (absolute body weight), height, gender, and race. Gender was coded as a dichotomous variable. Race was coded as a dichotomous variable based on whether or not patients were caucasian.

2.1.10 Risk indicators for thrombocytopenia

A set of risk indicators (variables) previously identified as being associated with thrombocytopenia (Bonfiglio *et al.*, 1995; Baughman *et al.*, 1993; Hanes *et al.*, 1997; Cawley *et al.*, 1999; Stephan *et al.*, 1999), along with other potential risk indicators identified from the literature were followed and recorded in the database. There were 24 and 126 potential risk indicators investigated for the baseline and ICU/CCU models, respectively. In this study, the term risk indicator (also called risk marker) was used instead of risk factor to identify certain characteristics that are associated with an increased risk of developing thrombocytopenia, because it has not been clearly demonstrated that these characteristics are causally associated with this condition (Kraemer *et al.*, 1997; Last, 1995).

Potential risk indicators were documented up to the time of thrombocytopenia, or for the entire duration of ICU/CCU stay for each patient who did not develop thrombocytopenia. Some of the potential risk indicators have not been previously reported to be associated with the development of thrombocytopenia. However, since these risk indicators are related to severity of illness, exposure to foreign surfaces, or invasive procedures, they were examined for their association with the development of thrombocytopenia. Potential risk indicators were categorized as indicated below.

For all dichotomous variables, the presence of a dichotomous risk indicator was designated by a "1" and the absence of that risk indicator was designated as a "0".

2.1.10.1 Patient demographics

Age[2], gender[2], Acute Physiology score (APS)[2] (Cawley *et al.*, 1999), Acute Physiology and Chronic Health Evaluation (APACHE II) score[2] (Cawley *et al.*, 1999; Stephan *et al.*, 1999), and alcohol

[2] Baseline risk indicators

history[2] were investigated as risk indicators for the development of thrombocytopenia. They were documented for each study patient. Age, APS, and APACHE II Score were classified as continuous variables, whereas gender, and alcohol history were classified as dichotomous variables.

2.1.10.1.1 Acute Physiology Score (APS) and Acute Physiology and Chronic Health Evaluation (APACHE II) Score

The APS and APACHE II are predictive instruments of outcome (mortality) in critically ill patients. The APS (Appendix 3) is a component of the APACHE II score. It is a weighting system, based on a scale of 0 to 4, used to assess the severity of acute disease (Knaus *et al.*, 1985). The APS is comprised of the sum of the weightings for 12 physiologic measures. It is determined from the worst physiologic value during the initial 24 hours after ICU/CCU admission. If a patient was transferred from another hospital or ICU, the APS was determined upon admission to LGH ICU/CCU. If any physiologic measure used for calculating the APS was missing, it was assumed to be normal and given a value of zero.

The APACHE II (Appendix 3) is a clinician-evaluated instrument used to stratify acutely ill patients based on the severity of disease (Knaus *et al.*, 1985). It is based on the premise that the severity of acute disease can be measured quantitatively by assessing the degree of abnormality of various physiologic measures. The APACHE II score represents the sum of weights assigned to 12 physiologic measures (APS), to age, and to a value for chronic health problems. Measurement of the 12 physiologic measures (APS) is also based on the worst value during each patient's initial 24 hours in the ICU/CCU. Age and severe chronic health problems more or less reflect a patient's diminished physiologic reserve, and thus, they have been incorporated into the APACHE II score.

2.1.10.1.2 History of alcohol use

Excessive alcohol use has been suggested to be a risk indicator for thrombocytopenia (Bogdonoff *et al.*, 1990). History of excessive alcohol use was determined when there was evidence of a history of

[2] Baseline risk indicators

alcoholism or consumption of 3 or more alcohol drinks daily. The necessary information was obtained from the medical chart, discussions with the patient or family, or the attending physician.

2.1.10.2 Medications as risk indicators for thrombocytopenia

Medications identified in previous studies (Bogdonoff, 1990; Hanes *et al*, 1997; Bonfiglio *et al*, 1995; Baughman *et al*, 1993) and/or in hematology (Williams, 1995) and internal medicine (Handin, 1994) textbooks as risk factors for thrombocytopenia were selected as potential candidate variables for the study. However, only those medications that were on formulary at LGH were selected for the analysis. The study investigators documented previous heparin use, including heparin-related products, which the patient was receiving or received prior to admission to the ICU/CCU. This was determined by reviewing the patient's medical chart, hospital pharmacy records, the provincial prescription database, and interviewing the family physician, patient and/or the family, where possible.

Medications previously identified as potential risk indicators for thrombocytopenia and on formulary at LGH included: heparin, vasoactive agents (epinephrine, norepinephrine, dopamine (at dose rates > 2 mcg/kg/min), isoproterenol, phenylephrine, and dobutamine), amrinone, auranofin (po), aurothianalate (iv), beta-lactam antibiotics (amoxicillin, ampicillin, cloxacillin, penicillin G, penicillin V, piperacillin, ticarcillin, cefaclor, cefamandole, cefotaxime, cefazolin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cephalexin), vancomycin, amakacin, gentamicin, neomycin, tobramycin, antifungal agents (amphotericin B, flucytosine, fluconazole, ketoconazole), antineoplastic agents, H_2-antagonists (cimetidine, ranitidine, and famotidine), thiazide (Aldacthiazide®, chlorthalidone, Dyazide®, hydrochlorothiazide, metolazone) and loop (ethacrynic acid, furosemide) diuretics, phenytoin, salbutamol, ipratropium bromide, quinidine, quinine, sulfonamide derivatives (acetazolamide, trimethoprim-sulfamethoxazole, azogantrisin, thiazides, furosemide, sulfadiazine, sulfasalazine, sulfinpyrazone, sulfisoxazole, olsalazine, acetohexamide, chlorpropamide, tolbutamide, gliclazide, glyburide), digoxin, methyldopa, tinzaparin, ASA, and NSAIDS (diclofenac, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen).

Single doses of some medications have been reported to be associated with thrombocytopenia (Williams, 1995). This usually follows re-exposure to the medication, but the initial exposure may have been hours earlier or a gradual exposure over months or years (Bogdonoff *et al.*, 1990; Williams, 1995). In general, since many patients admitted to an ICU/CCU have had previous hospital admissions, and because many of these patients have previously received drug therapy, the minimum exposure for inclusion was one dose prior to thrombocytopenia.

All medications identified *a priori* as possible risk indicators were recorded as either being administered or not. Therefore, each medication was classified as a dichotomous variable. Individual patients were classified as either being exposed to a specific medication, designated by a "1" or not being exposed to that medication, represented by a "0".

It was anticipated that there would be some medications that patients would not be exposed to, or some medications that few (< 5) patients would be exposed to. These medications could not be used in the analysis because of a zero cell count or less than 5 cases in a cell in a contingency table. Therefore, classes of medications were constructed and entered into logistic regression analysis. Each class of medication was analyzed as a dichotomous variable. Medications that one or more patients were exposed to were grouped into the following classes:

1. Penicillin antibiotics (ampicillin, cloxacillin, penicillin G, pipercillin)
2. Cephalosporins (cefotaxime, cefazolin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime)
3. Histamine H_2-Antagonists (cimetidine, ranitidine)
4. Inotropes (dobutamine, dopamine, norepinephrine)
5. Sulfonamide derivatives (acetazolamide, trimethoprim-sulfamethoxazole, dyazide, furosemide, gliclazide, glyburide, metolazone)

Dosages, total duration of use, route of administration, medication frequency, and indication for use were only recorded for heparin. In addition, the number of medications each patient was exposed to in the ICU/CCU prior to the development of thrombocytopenia was recorded. If the patient did not

develop thrombocytopenia, the total number of medications the patient was administered was also recorded.

The possible association of heparin with the development of thrombocytopenia was explored further by analysing the daily dose of heparin administered to patients. Heparin exposure was categorized as follows: 1) full anticoagulation (high dose) for thrombosis therapy (> 16,000 units/day); 2) prophylactic doses (medium dose) (1,000-16,000 units/day); and 3) doses to maintain IV line and pulmonary artery catheter patency (low dose) (< 1,000 units/day).

2.1.10.3 Admission and most responsible diagnoses

The admission diagnosis[2] for patients was taken from the ICU nurses daily monitoring form and categorized as outlined below. As patients' clinical course evolved in the ICU, a different diagnosis sometimes became the predominant reason for the ICU stay. This was included in the discharge notes as the primary discharge diagnosis. This diagnosis was taken from the chart for each patient and designated as the most responsible diagnosis for the ICU stay (when it occurred before thrombocytopenia), based on the categories described below. The admission and most responsible diagnoses were used in the development of 2 different multivariate logistic regression models. Each diagnosis was classified as a dichotomous variable. The following diagnostic categories were used:

1. Nervous System[2] (neurologic)
   - Includes surgical and non-surgical disorders, head trauma, and seizures
2. Respiratory Surgery[2]
   - Includes all respiratory related surgeries, such as lobectomy, pneumoectomy, mediastinectomy

[2] Baseline risk indicators

3. Respiratory Non-Surgery[2]
    - Bronchitis/asthma, chronic obstructive pulmonary disease (COPD), pulmonary edema, respiratory failure, acute respiratory distress syndrome (ARDS), and other respiratory disorders (not including ones just mentioned)
4. Vascular Surgery[2]
    - Includes all vascular surgeries, such as aortic-femoral bypass surgery and aortic abdominal aneurysm surgery
5. Cardiovascular Non-Surgery[2]
    - Congestive heart failure(CHF), rhythm disturbances, or other cardiovascular disorders, but not acute myocardial infarction or unstable angina
6. Acute Myocardial Infarction (AMI)[2]
    - Physician documented AMI coinciding with the appearance of CK-MB (creatine kinase MB isoenzyme) in serum within 3 to 4 hours after AMI and electrocardiogram (ECG) changes such as ST-segment elevation and/or presence of Q waves
7. Unstable Angina[2]
    - Physician documented unstable angina coinciding with no CK-MB isoenzyme and ECG changes consistent with myocardial ischemia including non-specific ST-T changes,T-wave inversion, or ST-segment depression
8. Gastrointestinal (GI)[2]
    - GI procedures and all GI disorders (including hepatobiliary and pancreatic disorders) except GI bleed
9. Musculoskeletal and Connective Tissue[2]
    - Any trauma, injury or wound to the musculoskeletal system or any disease process that involved the connective tissue as determined by the attending physician.

[2] Baseline risk indicators

10. Endocrine and Nutrition[2]
11. Diabetes Mellitus[2]
    - Includes diabetic ketoacidosis
12. Kidney, Urinary Tract, and Reproductive Disorders[2]
13. Infections[2] (excluding sepsis)
    - Defined as patients with clinical signs (temp > 38.5 °C, WBC > 11 × 10^9/L), or those given antibiotics for the infection, excluding those with sepsis
14. Malignancy[2]
15. Drug Overdose/Poisoning[2]
16. Sepsis[2]
    - The diagnosis of sepsis was noted if the physician recorded the diagnosis in the chart and if the patient manifested 2 or more of the following conditions: temperature greater than 38°C or less than 36°C, respiratory rate greater than 20 breaths/minute, heart rate greater than 90 beats/minute, or partial pressure of carbon dioxide below 32 mm Hg, and white blood cell count greater than 12 × 10^9/L or less than 4 × 10^9/L (Bone *et al.*, 1992). Also included in this definition of sepsis were patients with severe sepsis (sepsis associated with organ dysfunction, hypoperfusion, or hypotension) and septic shock (sepsis-induced hypotension along with perfusion abnormalities or organ dysfunction in spite of adequate fluid resuscitation)
17. Gastrointestinal Bleed[2]
    - Physician documented GI bleed

2.1.10.3.1 Admission and most responsible diagnoses classified as ICU or CCU diagnoses

Patients admitted for an acute myocardial infarction, unstable angina, or cardiovascular non-surgery were classified as CCU patients. Patients who were diagnosed with the other 14 diagnostic

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[2] Baseline risk indicators

categories were classified as ICU patients.

2.1.10.4 Organ function and risk of thrombocytopenia

The following changes in organ function have been reported to be associated with thrombocytopenia in previous studies (Bonfiglio *et al.*, 1995; Baughman *et al.*, 1993) and were included in the analysis.

2.1.10.4.1 Renal dysfunction

Baseline and daily serum creatinine concentration, when available, were recorded and creatinine clearance was determined by the modified Cockcroft and Gault equation normalized for weight. (Cockcroft and Gault, 1976). Estimated creatinine clearance $\leq$ 30 μmol/min/72kg or a 50% drop in creatinine clearance was considered abnormal.

2.1.10.4.2 Hepatic dysfunction

Baseline and daily liver function test results, when available, were recorded. Aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and alkaline phosphatase (ALK) were considered elevated when their values exceeded 5 times the upper limit of the normal range (Bonfiglio *et al.*, 1995). Total and direct bilirubin were considered elevated when their values exceeded 3 times the upper limit of the normal range. In addition, INR was also documented, when available, for patients who were not receiving any anticoagulant therapy.

Both renal and hepatic dysfunction were classified as dichotomous variables.

2.1.10.5 Medical procedures as risk indicators for thrombocytopenia

The following medical procedures were documented either until the development of thrombocytopenia or the end of ICU/CCU stay when no thrombocytopenia occurred: units of packed red blood cells transfused (Hanes *et al.*, 1997; Baughman *et al.*, 1993), units of fresh frozen plasma

transfused, surgery (Hanes *et al.*, 1997), surgery within 24 hours of ICU/CCU admission[2] (Hanes *et al.*, 1997), pulmonary artery (Swan-Ganz) catheter insertion (Bonfiglio *et al.*, 1995; Bogdonoff *et al.*, 1990) or central venous catheter placement, or cardiac valve prosthesis (Bogdonoff *et al.*, 1990). In addition, mechanical ventilation was documented and included in the analysis. Each procedure was classified as a dichotomous variable.

2.1.10.6 Admission platelet count and hemoglobin concentration as risk indicators for thrombocytopenia

The admission platelet count[2] and hemoglobin concentration[2] were recorded for each patient eligible for the study. If the admission platelet count and hemoglobin concentration were obtained in the emergency department, they were used, provided the patient was brought to the ICU/CCU within 6 hours. If the patient was transferred from a ward or from another hospital to the unit, the admission platelet count and hemoglobin concentration were the first obtained in the ICU/CCU. The admission platelet count and hemoglobin concentration were classified as continuous variables.

2.1.11 Clinical outcomes

Outcome data, such as the incidence of hemorrhage or thrombosis, as defined by the attending physician using routine clinical criteria for diagnosis and assessment, were documented for the entire duration of hospital stay. DIC, ITP, and TTP were also to be noted according to the physician's diagnosis. This information was recorded prospectively during the ICU/CCU stay, and charts were examined retrospectively for events occurring during the entire hospital stay, but after discharge from the ICU/CCU. In addition, duration of ICU/CCU stay prior to thrombocytopenia, as well as total length of stay on the unit until discharge or death, were documented. Total duration of hospital stay was also noted. Furthermore, patient mortality during the ICU/CCU and hospital stay was recorded. The number of patients in whom heparin was discontinued as a result of thrombocytopenia was also noted (i.e. as noted by the physician or when ordered within 24 hours of the occurrence of thrombocytopenia).

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[2] Baseline risk indicator

2.2 STATISTICAL ANALYSIS

2.2.1 Data management

All analyses were performed using SPSS® 9.0 Professional version. This included all univariate procedures, logistic regression analyses, and ROC curve generation. Figures were generated using Slidewrite® 4.0 32-bit edition.

2.2.2 Potential risk indicators for thrombocytopenia

2.2.2.1 Descriptive analysis

Baseline demographic characteristics of the study population were summarized in terms of the mean and standard deviation (SD) for continuous variables and frequencies for dichotomous variables. Continuous data were analyzed using Student's t-test for independent samples. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

2.2.2.2 Logistic regression

Logistic regression is based on the principle of regressing a dichotomous dependent variable on a set of independent covariates (risk indicators) (Hosmer and Lemeshow, 1989). In the present study, logistic regression analysis was used to examine the individual and combined relations between the dichotomous (binary) outcome of thrombocytopenia and an *a priori* list of risk indicators during a patient's stay in the ICU/CCU. The goal of the logistic regression analysis was to achieve a predictive mathematical model that described the relation between thrombocytopenia and a set of independent variables.

2.2.2.2.1 Coding of independent variables

Independent variables were coded either as dichotomous or continuous, as indicated above. Continuous variables with a low frequency of occurrence were recoded as dichotomous variables. For

example, units of packed red blood cell (PRBC) and fresh frozen plasma (FFP) transfusions were recoded as "1" if a patient received a transfusion or "0" if a patient did not receive a transfusion. Continuous variables were entered without modification, with the exception of admission platelet count and hemoglobin concentration, and age, which were expressed as multiples of 50×10^9/L, 25 g/L, and 5 years, respectively.

2.2.2.2.2 Univariate analysis

Univariate analysis was used to reduce the initial variable list by identifying those variables that might be individually associated with thrombocytopenia. These variables were considered in the development of multivariate models. For dichotomous variables, univariate analysis was performed with the chi-square test, whereas for continuous variables, analysis involved fitting a univariate logistic regression model to obtain the level of significance by the Wald statistic. Variables selected as candidates for multivariate logistic regression required a p-value ≤ 0.25 by the appropriate univariate test. Variables that exceeded this criterion, but were thought to be clinically important were also selected. Variables with small numbers in each group (exposure frequency less than 5%) were eliminated from consideration as candidates for multivariate logistic regression.

2.2.2.2.3 Collinearity between risk indicators

Independent variables were considered to demonstrate a high degree of association if they conveyed essentially the same information regarding the risk of thrombocytopenia. The strength of association was indicated by the size of the correlation coefficient. This was done by correlating each independent variable identified by univariate analyses with each of the other variables using the bivariate correlation procedure in SPSS®. Pearson correlation coefficients range from – 1.0 to + 1.0, and a coefficient of zero indicates that there is no association between the two variables. Variables were considered to demonstrate collinearity when the Pearson's correlation coefficient was greater than 0.7. The more clinically relevant of two collinear variables was chosen for inclusion in the multivariate analyses.

2.2.2.2.4 Linearity of continuous variables

Continuous variables were assumed to be linear in the logit (log-odds) at the variable selection stage. Once the variable was identified as important by univariate logistic regression (Wald's statistic), the correct scale or parametric relation was determined. This was done by determining the quartiles of the continuous independent variable and creating three design or dummy variables using the lowest quartile as the reference group. The design variables were then used in the multivariate model in place of the continuous independent variable.

To establish the scale of the continuous variable, the estimated coefficients of the three design variables were plotted against the midpoint of each quartile. The plot was then examined for either an increasing or decreasing linear trend in the estimated coefficients.

2.2.2.2.5 Method of independent variable entry for multivariate logistic regression

Multivariate logistic regression was selected as an appropriate statistical technique, due to the dichotomous nature of the dependent variable (thrombocytopenia). It was used to identify independent associations between risk indicators and thrombocytopenia after adjusting for other variables. Variables (risk indicators) identified by univariate analyses were entered into a multivariate logistic regression model by the backward stepwise method. The backward stepwise method involves backward elimination followed by a forward selection at each step. In brief, all eligible variables are entered into the model together at the first step. Each variable is then tested for removal, one by one, using the likelihood ratio test as the test statistic. The removal of a variable from the model is based on the significance of the change in the log likelihood. This is accomplished by estimating the log likelihood of the model with and without the variable. The variable with the largest p-value, greater than a probability of 0.10 ($p_{out} > 0.10$) of the likelihood ratio statistic to remove a variable, is removed from the model. The maximum number of iterations to obtain the maximum likelihood estimates at each step was set at 20 (default value in SPSS® 9.0). After the first variable is removed, each variable is again tested for removal, and the one with the largest p-value is removed. After this step, the two variables excluded from the model are tested for possible entry, based on the significance level of the Score test statistic (a test statistic very similar to

the likelihood ratio test). The variable with the lowest p-value, provided it is less than a probability of 0.05 ($p_{in} < 0.05$), is added to the model. Variables in the model are then evaluated again for stepwise removal and entry until no more variables meet removal ($p_{out} = 0.10$) or entry ($p_{in} = 0.05$) criteria, or when the current model is the same as a previous one. All variables in the final model should have a p-value (based on the Wald test statistic, which is very similar to the likelihood ratio test) less than 0.10.

The estimated coefficients (maximum likelihood estimates), their standard errors, the Wald test statistic and associated p-value (based on a chi-square distribution), odds ratio [calculated as exp (β)], and 95% confidence intervals around the estimated odds ratio of thrombocytopenia were calculated. Lastly, a mathematical expression relating the independent risk indicators to the logit (log odds of developing thrombocytopenia) was expressed. By solving the mathematical expression, the predicted probability of a patient developing thrombocytopenia can be determined.

2.2.2.2.6 Interaction terms in the model

An interaction between two variables occurs when the effect of one of the variables is not constant over levels of the other. Following selection of the essential variables for the main effects model, interactions between these variables were checked (Hosmer and Lemeshow, 1989a). This was accomplished by first creating an interaction term, which involved taking the product of the two variables involved. SPSS® performed this computation automatically. The interaction term was then assessed for its contribution to the model (significance) by using the likelihood ratio test. Decisions on inclusion of interaction terms were based on model statistics as well as clinical considerations.

2.2.2.2.7 Assessing the fit of the model

The Hosmer-Lemeshow goodness of fit test was used to evaluate how well the model described the observed data. This test is based on the null hypothesis that the model is a reasonable fit of the observed data. SPSS® was used to generate the Hosmer-Lemeshow goodness of fit test statistic. In brief, the test statistic was obtained by forming ten groups of equal size containing the deciles of the fitted values. Observed and expected values were calculated by summing the estimated probabilities and

observed values of thrombocytopenia. This test statistic approximately follows a chi-square distribution with eight degrees of freedom. Since the null hypothesis states that the model is a reasonable fit of the observed data, a p-value, computed from the chi-square distribution, greater than 0.05 is required in order to fail to reject or to "accept" the null hypothesis that the model is a reasonable fit.

2.2.2.2.7.1 Sensitivity and specificity of the models

The sensitivity, specificity, and overall classification of the model were also used to assess how well the model fit the observed outcome. The sensitivity of a model was the proportion of patients observed to have developed thrombocytopenia that the model correctly predicted to have developed thrombocytopenia. A model's specificity was the proportion of patients who were not observed to have developed thrombocytopenia that the model correctly predicted not to have developed thrombocytopenia. The overall correct classification of a model was the proportion of 362 patients correctly predicted to have and not have developed thrombocytopenia. This classification is based on a cutoff or decision threshold of 0.50, which means that if a patient's predicted probability was ≥ 0.50, he/she would be predicted to develop thrombocytopenia. A model's sensitivity, specificity, and overall correct classification were obtained from the classification table in the SPSS® logistic regression printout.

2.2.2.2.8 Regression diagnostics

Regression diagnostics were used to examine how well the model described the observed data and the impact of individual patients in the model. A casewise listing of the values of the following variables was created in SPSS®: predicted probability, deviance, residual, standardized (normalized) residual, studentized residual, leverage value, Cook's distance, and difference in beta. These measures were investigated in order to identify individual patients who did not fit the model well (outliers) and whose data may have had a strong influence on the coefficient estimates. This gave an indication of how well the model fit the observed data and how sensitive the model was to individual patient's data. The predicted probability was the probability (expected value) for each case developing thrombocytopenia.

2.2.2.2.8.1 Residual analysis

The residual is the difference between the observed probability of thrombocytopenia (in this case "0" or "1") and the predicted probability of thrombocytopenia based on the model. The studentized residual was used to identify patients whose observed outcome was not very close to the model based predicted probability of their outcome. These patients were expected to have a large error or residual. The studentized residual for a particular case is the change in the model deviance (see below) when that case is excluded. The studentized residual was plotted against the predicted probability. As a rule of thumb, 99% of the data should be within ± 3 standard deviations (SD) from the mean of the residuals (Draper and Smith, 1981). This rule is based on the approximate normality of the residuals.

2.2.2.2.8.2 Leverage plots

Leverage was used to identify patients who may have had a covariate pattern (a single set of values for the covariates in the model) that was unusual relative to the rest of the patients. The leverage value is defined as the relative influence of each observation on the model's fit. Leverage values were used to detect observations that had a large effect on the predicted probabilities. The leverage values were plotted against the predicted probability to detect extreme cases.

2.2.2.2.8.3 Influence of individual cases

The effects of residual analysis and leverage are combined to generate a diagnostic that expresses the influence of each patient on the estimated coefficients (Hosmer and Lemeshow, 1991). These cases have a large effect on the magnitude of the estimated coefficients in the model. Cook's distance and difference in beta coefficients were used to identify influential cases. Cook's distance is defined as a measure of the influence of a case. It was used to approximate the overall change in the estimated coefficients due to the exclusion of the *i*th patient (Hosmer and Lemeshow, 1991). Difference in beta coefficients was also used to measure influence. It measures the difference in the estimated coefficients for each independent variable when the case is omitted from the model. Both variables were plotted

against the predicted probability. Large values for either Cook's distance or difference in beta coefficients identified cases that were examined further.

2.2.2.2.8.4 Examination of problematic cases

Cases identified as outliers and/or influential by regression diagnostics were checked for correct entry of data and correct coding into the Access 7.0® database and SPSS 9.0®.

2.2.2.2.9 Evaluation of the proportion of explained variation

The proportion of variation (R^2) in the dependent variable, thrombocytopenia, explained by the variables in the model was calculated using SPSS®. Two R^2 values were given: the Cox & Snell (R_C), which achieves a maximum value of 0.75, and the Nagelkerke (R_N), which transforms the R_C so that it has a maximum value of 1.

The Pearson correlation (r) was also calculated and then squared to describe the association between observed and predicted outcomes. The occurrence of thrombocytopenia (observed outcome) was correlated with the predicted probability of an event occurring. A correlation coefficient, r, was determined by the bivariate correlation procedure in SPSS®. It is a number between –1 and 1 which reflects the degree of association between the observed outcome and the predicted probability (Zar, 1994).

2.2.2.3 Predictive ability of the models using a receiver operating characteristic (ROC) curve

The predictive ability of the model was assessed by the area under the receiver operating characteristic (ROC) curve. A ROC curve illustrates the relation between sensitivity and specificity. In brief, the predictive ability of the model was evaluated for its ability to discriminate between patients who are likely to either develop or not develop thrombocytopenia by comparing the predicted probability of thrombocytopenia to the observed frequencies over a number of decision thresholds. A decision threshold represents a specific predicted probability. Since the predicted probability of thrombocytopenia has continuous values from 0 to 100 percent (0 to 1.0), a decision threshold was chosen to classify the patient as predicted to develop thrombocytopenia and not predicted to develop thrombocytopenia. A

number of decision thresholds were selected. For instance, the frequency of false-positives (patients predicted to develop thrombocytopenia who actually did not) was reduced by selecting a higher decision threshold. For each decision threshold, a classification table was constructed of the model's predicted probabilities of developing or not developing thrombocytopenia versus the observed (true) outcome of thrombocytopenia (Y = 0 or Y = 1). For example, if a decision threshold of 0.50 (50%) was chosen, any patient with a predicted probability of developing thrombocytopenia greater than or equal to 0.50 would be categorized as predicted to develop thrombocytopenia. At different decision thresholds, values for sensitivity (true-positive) and specificity (true-negative) were calculated by comparing predicted probabilitites and observed outcomes with the actual presence or absence of thrombocytopenia for each patient. For each decision threshold, the sensitivity and 1 – specificity values, which represent one point, were plotted and a ROC curve was generated. This pair or point was plotted as the "y" and "x" coordinate values on a graph, respectively. The axes of the graph ranged from 0 to 1 because these are the limits of possible sensitivity and specificity values. A stepwise curve was then drawn through the plotted points to produce the ROC curve.

The area under the ROC curve or c index, was determined from the Dorfman and Alf maximum likelihood estimation program. It represents the probability of correctly ranking a randomly selected pair of thrombocytopenic and non-thrombocytopenic patients (Hanley and McNeil, 1982). In other words, it is the probability that a patient with thrombocytopenia has a higher predicted probability than a patient without thrombocytopenia.

RESULTS

3.1 DEMOGRAPHIC CHARACTERISTICS OF STUDY SAMPLE AND CLINICAL COURSE IN THE ICU/CCU

3.1.1 Patient demographic characteristics

Between June 11, 1997 and June 11, 1998, 935 patients were admitted to the Lions Gate Hospital's ICU/CCU. Of these, 362 fit the criteria for inclusion in the study. Five hundred and seventy-three patients were excluded for the following reasons: 432 had less than 2 platelet counts, 78 had an admission platelet count less the 150×10^9/L, 24 were repeat admissions to the unit, 21 had 2 platelet counts measured within 12 hours, 11 were enrolled in another study that randomly assigned patients to receive heparin or hirudin, 5 were less than 18 years of age, and 2 were admitted with disseminated intravascular coagulation (DIC).

Table 3 summarizes the admission demographic characteristics of the 362 study patients. The study sample had a mean age of 63.2 years, and was mainly comprised of males and caucasians. Figure 1 illustrates the age distribution of the 362 study patients, and Figure 2 shows the age distribution among patients with an ICU and CCU diagnosis. The age distribution for patients with an ICU diagnosis was more negatively skewed. The mean lengths of ICU/CCU and hospital stay for the 362 patients were 6.0 days and 17.8 days, respectively. The median lengths of ICU/CCU and hospital stay for the 362 patients were 3.0 days and 10.0 days, respectively.

3.1.1.1 Severity of illness

The mean Acute Physiology scores (APS) and APACHE II scores for all study participants were 11.3 (range 1-40) and 15.4 (range 3-46), respectively. In addition, the median APS and APACHE II scores were 7.0 and 12.0, respectively. The distributions of the APS and APACHE II scores are shown in Figures 3 and 4. In addition, the APACHE II score distribution among patients with an ICU and CCU

TABLE 3

DEMOGRAPHIC CHARACTERISTICS OF THE STUDY SAMPLE (N = 362)

Study Sample Characteristics	Number of Patients (%)	Mean ± SD	Range
Age (years)		63.2 ± 15.4	18-90
Gender			
Males	229 (63.4)		
Age		62.4 ± 15.0	18-90
Females	133 (36.7)		
Age		64.6 ± 15.9	19-88
Race			
Caucasian	317 (87.6)		
Non-Caucasian	45 (12.4)		
APACHE II score		15.4 ± 9.4	3-46
Acute Physiology Score		11.3 ± 8.9	1-40
Alcohol History	42 (11.6)		
Weight [actual body weight] (kg)		76.2 ± 17.2	39-135
Location patient admitted from			
Emergency room	242 (66.9)		
Ward	101 (27.9)		
Other hospital	19 (5.2)		

Figure 1 **Age Distribution of Patients in the ICU/CCU Study Sample**

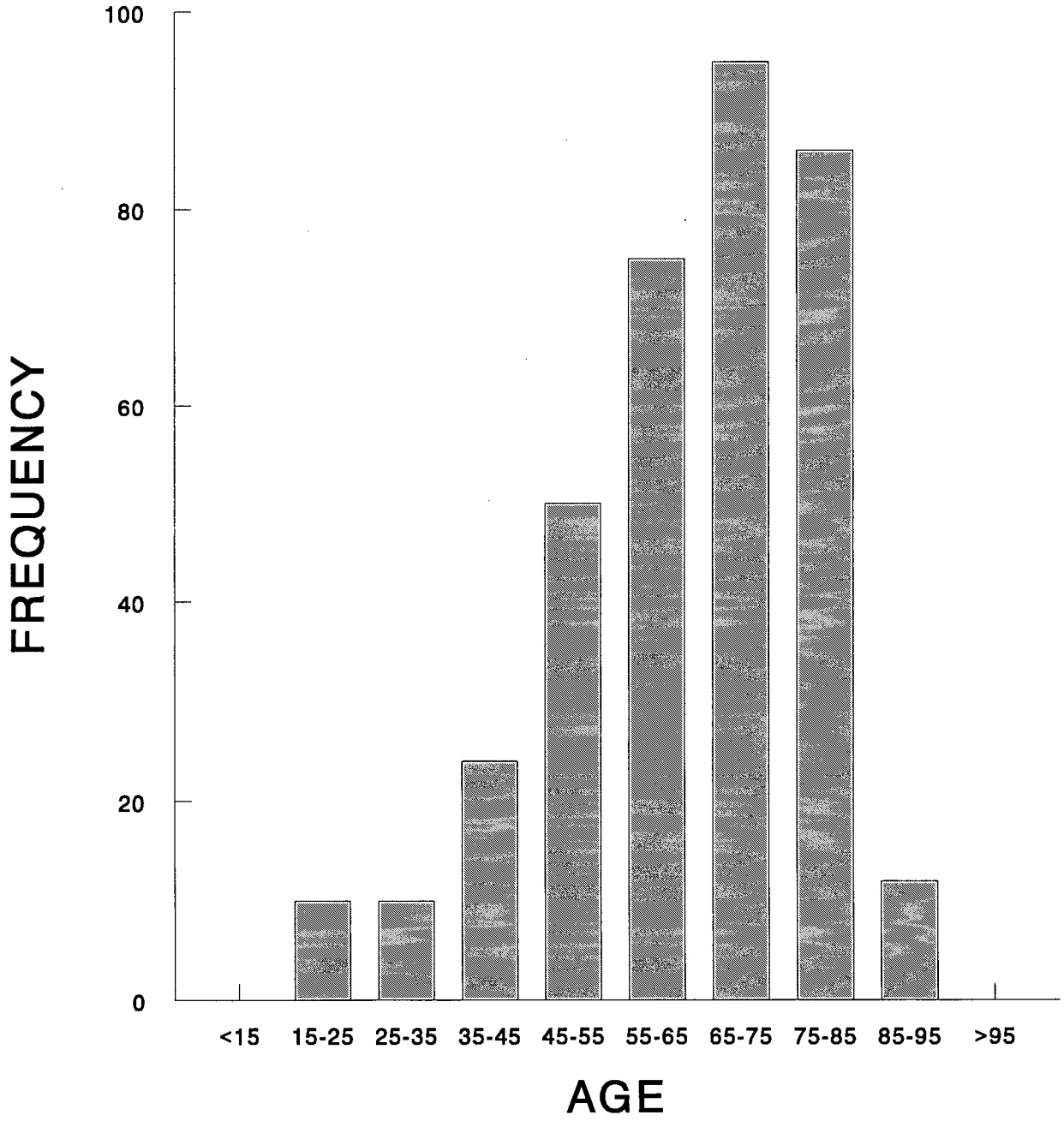


Figure 2 **Comparison of Age Distributions Among ICU and CCU patients**

ICU patients are indicated by solid black bars (N = 173) and CCU patients are indicated by light coloured bars (N = 189)

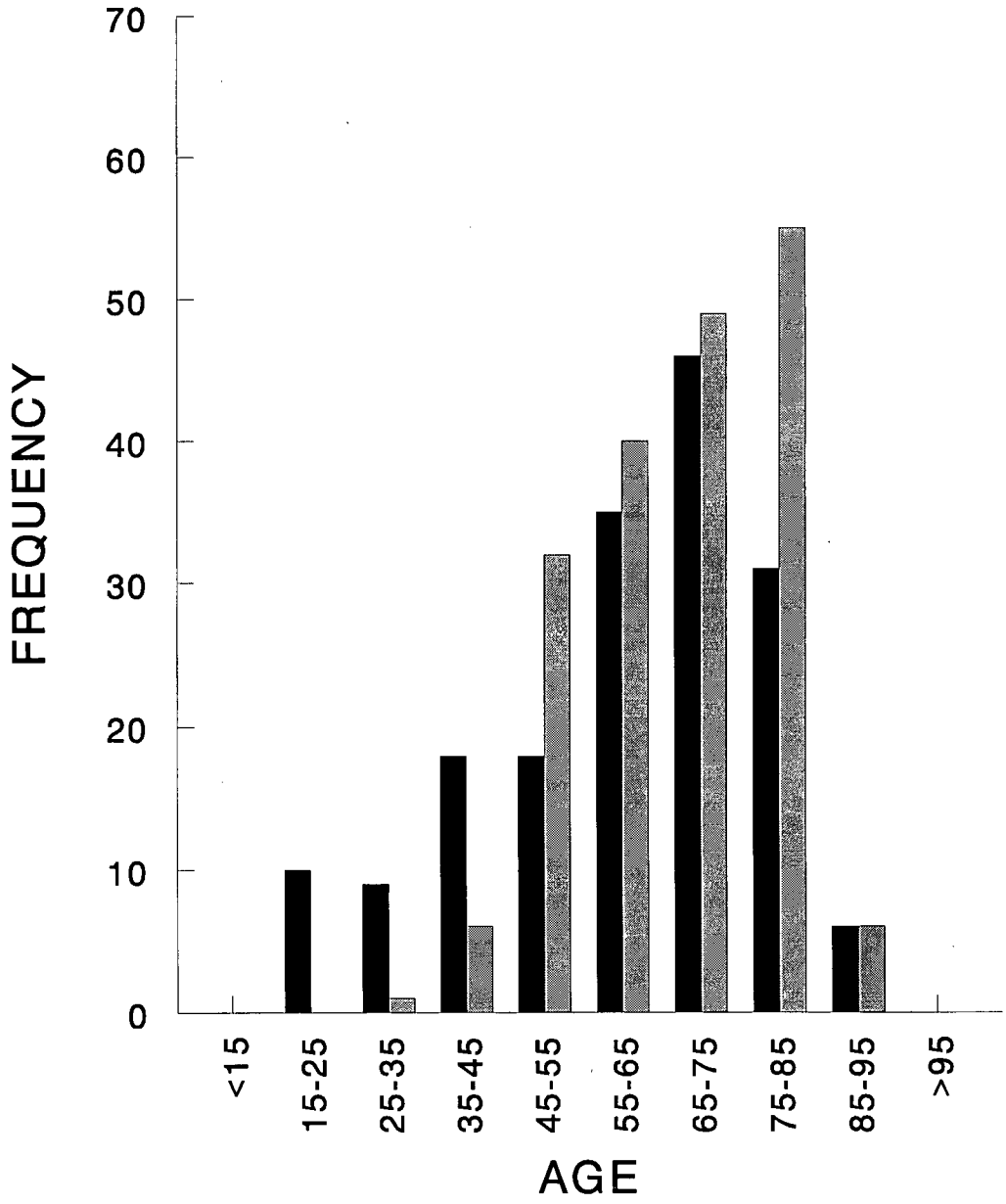


Figure 3 **Distribution of Acute Physiology Scores Among Patients in the ICU/CCU Study Sample**

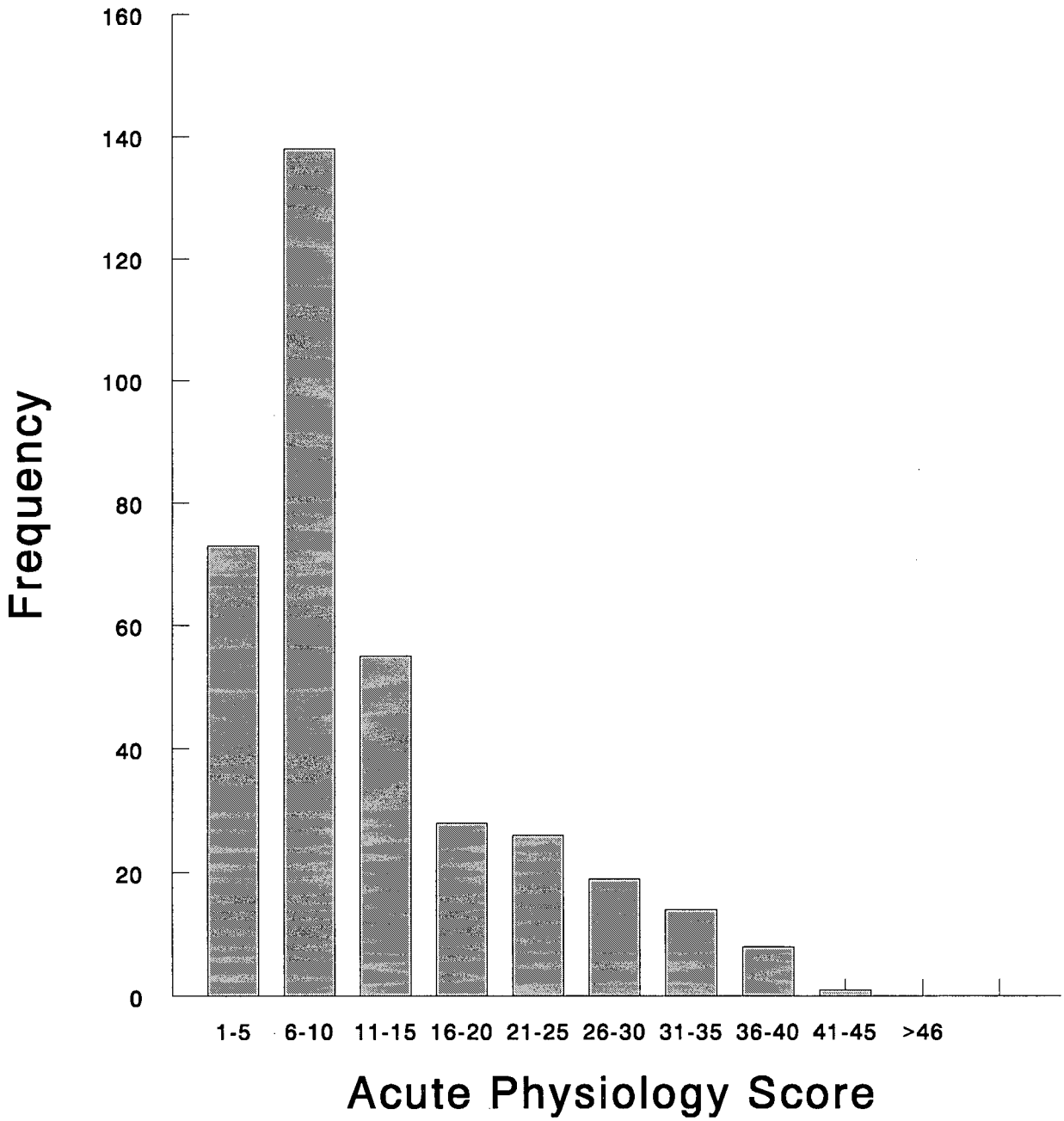


Figure 4 **Distribution of APACHE II Scores Among Patients in the ICU/CCU Study Sample**

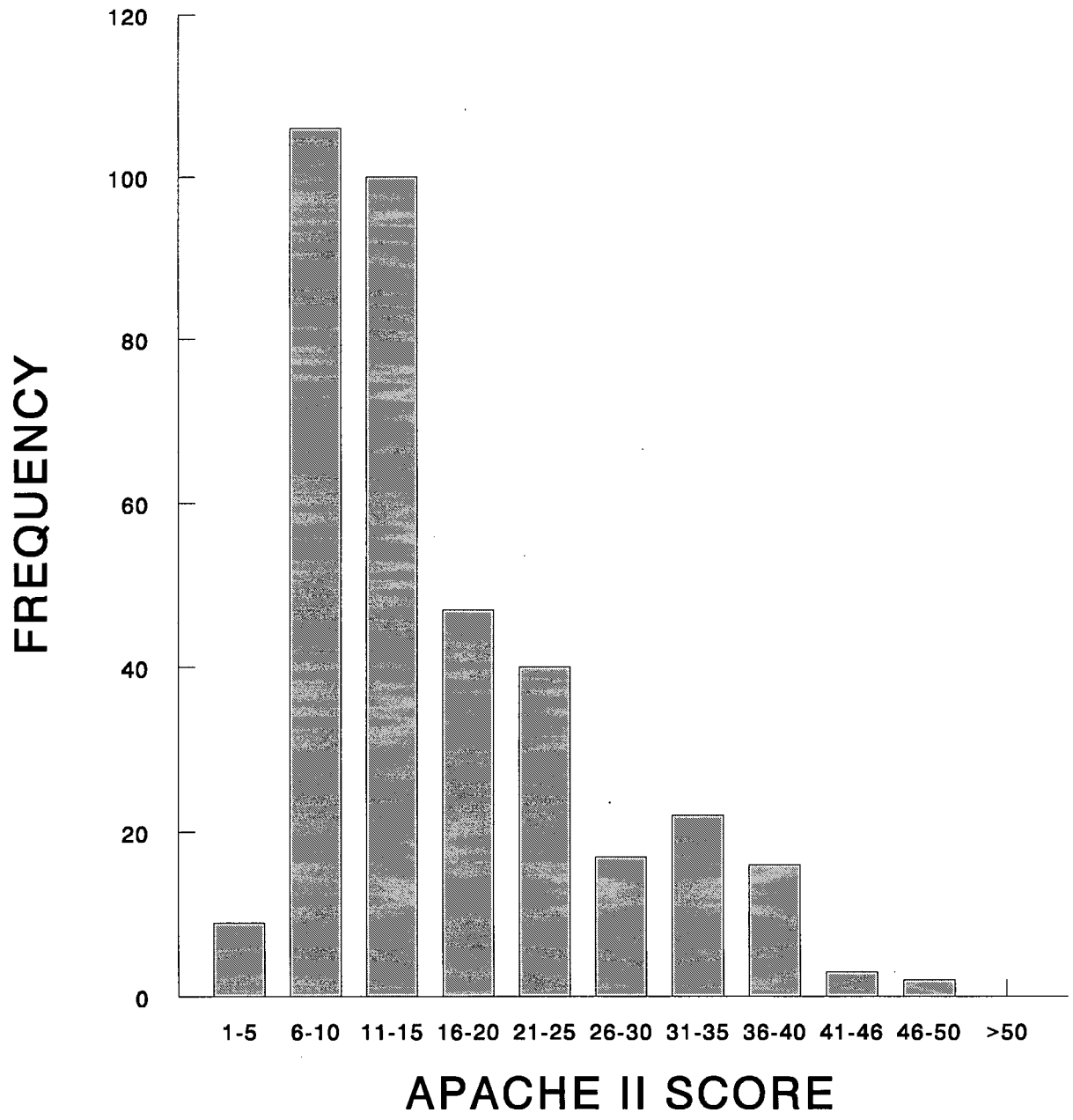
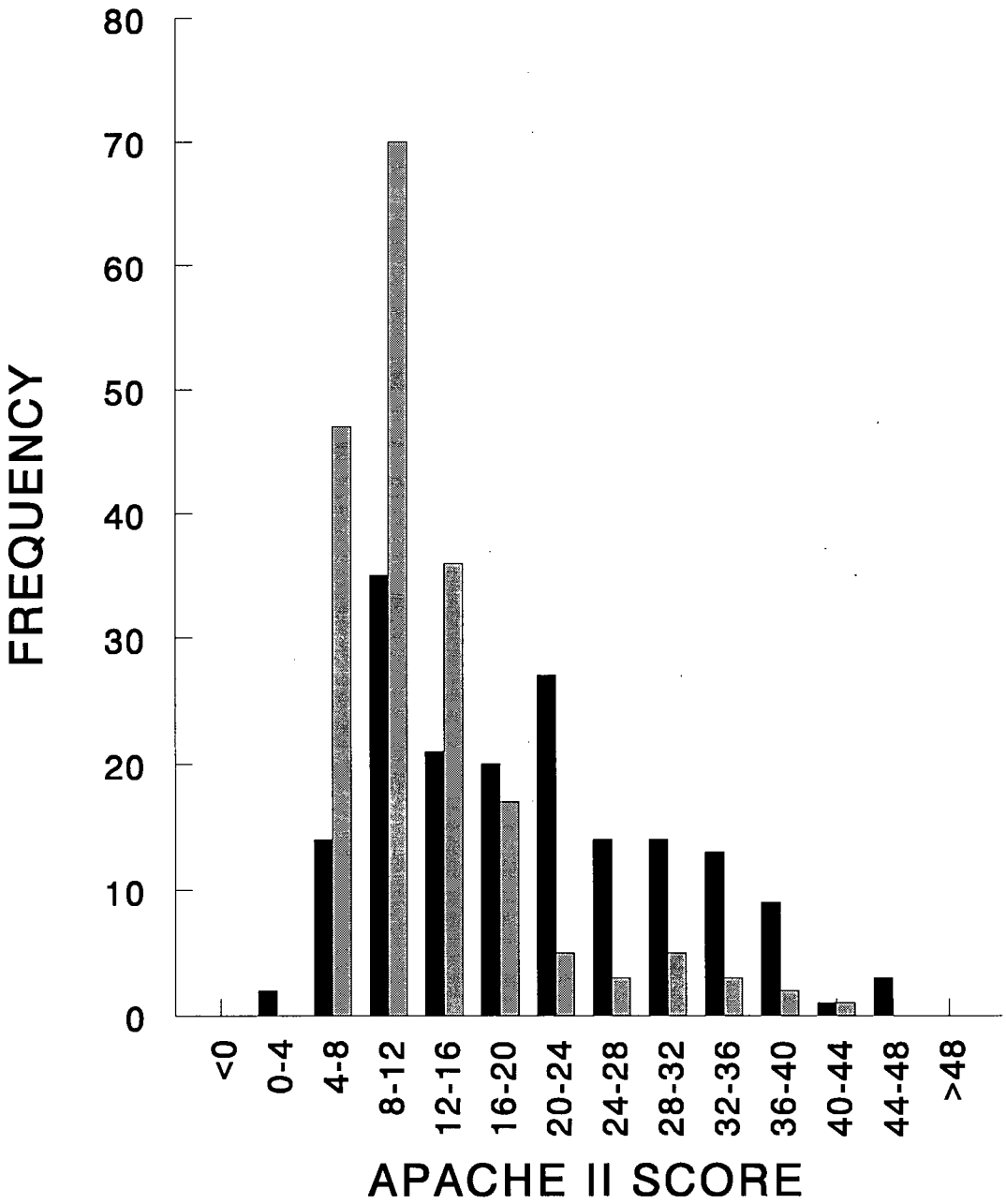


Figure 5 **Comparison of APACHE II Scores Distributions Among ICU and CCU patients**

ICU patients are indicated by solid black bars (N = 173) and CCU patients are indicated by light coloured bars (N = 189)



admission diagnosis is illustrated in Figure 5. The APACHE II scores for patients with an ICU diagnosis were more positively skewed. Based on the APACHE II scores, the patients comprising the study sample would be considered mildly to moderately critically ill.

3.2 ADMISSION AND MOST RESPONSIBLE DIAGNOSES, AND CLINICAL COURSE

3.2.1 Admission and most responsible diagnoses

The admission and most responsible diagnoses of the study patients admitted to the ICU/CCU are summarized in Table 4. Forty-eight of 362 (13.3%) patients had a most responsible diagnosis that was different than their admission diagnosis. In most of these cases, patients admitted with a diagnosis of unstable angina had a most responsible diagnosis of myocardial infarction or cardiovascular non-surgery (CHF). Nine patients had an admission diagnosis of sepsis. Four more patients with an admission diagnosis other than sepsis (e.g. 2 with infection, 1 respiratory non-surgery diagnosis, and 1 gastrointestinal diagnosis) had a most responsible diagnosis of sepsis during their stay on the unit. In addition, 11 patients had an admission diagnosis related to the nervous system. Three additional patients (2 respiratory non-surgery diagnoses and 1 cardiovascular non-surgery diagnosis) had a seizure on the unit, which increased their length of stay.

While the unit does not explicitly distinguish between ICU and CCU admission diagnosis based on the criteria stated in the methods (Section 2.2.10.3.1), the distribution of admission and most responsible diagnoses based on these criteria is shown in Table 5. Approximately half the admission and most responsible diagnoses were CCU diagnoses.

The mean APS and APACHE II scores for patients with an ICU admission diagnosis were 15.3 ± 9.6 and 19.3 ± 10.3, respectively. The median APS and APACHE II score for the same ICU patients were 13.0 and 18.0, respectively. Similarly, the mean and median APS and APACHE II score for patients with a CCU admission diagnosis were 7.6 ± 6.2 and 6 and 11.9 ± 6.8 and 10, respectively.

3.2.2 Admission platelet count

The mean admission platelet count (± SD) of the study sample was 246.2 ± 78.5 × 10^9/L (range 151 - 606 × 10^9/L). The mean minimum platelet count (± SD) of the 362 patient study sample during ICU/CCU stay was 192.6 ± 74.7 × 10^9/L (range 42 - 555 × 10^9/L).

3.2.3 Precision of platelet count determinations

The mean intra-day CV was 2.9%. The range of platelet counts for the 6 patients over the 4 days was 98 – 386 (× 10^9/L). For the 9 non-thrombocytopenic patients whose blood samples were assessed over 6 days, the mean inter-day CV of the platelet count was 10.5%. As this determination had to be done with a different sample each day the estimate of inter-day platelet count variability includes intra-patient variability and variability inherent in the method.

3.2.4 Clinical course in the ICU/CCU

3.2.4.1 Incidence of thrombocytopenia

The incidence of thrombocytopenia was determined for the 362 patients who met the inclusion criteria. Sixty-eight (18.8%; 95% CI: 14.8% - 22.8%) patients developed thrombocytopenia, defined as two consecutive platelet counts less than 150 × 10^9/L. The mean (± SD) onset of thrombocytopenia was 2.9 ± 4.0 days (range 1-34 days). Twenty-eight (7.7%) patients had only one platelet count less than 150 × 10^9/L, after which the platelet count rose above this threshold. These patients were not considered to have developed thrombocytopenia.

Mean admission platelet counts were 216.1 ± 65.7 and 253.2 ± 79.7 × 10^9/L ($p < 0.001$) in patients who did and did not develop thrombocytopenia, respectively. The mean minimum platelet counts were 110.6 ± 25.9 × 10^9/L and 211.6 ± 69.3 × 10^9/L ($p < 0.001$) for patients developing and not developing thrombocytopenia, respectively. This corresponds to a 48.8% and 16.4% lower platelet count from admission values for thrombocytopenic and non-thrombocytopenic patients, respectively.

TABLE 4

ADMISSION AND MOST RESPONSIBLE DIAGNOSES FOR THE STUDY SAMPLE

Diagnoses	Admission Diagnoses Number of Patients (%) [N = 362]	Most Responsible Diagnoses Number of Patients (%) [N = 362]
Acute myocardial infarction	95 (26.2)	98 (27.1)
Cardiovascular non-surgery	45 (12.4)	56 (15.5)
Respiratory non-surgery	57 (15.7)	52 (14.4)
Unstable angina	49 (13.5)	36 (9.9)
Infection	20 (5.5)	17 (4.7)
Gastrointestinal	14 (3.9)	15 (4.1)
Nervous system	11 (3.0)	14 (3.9)
Sepsis	9 (2.5)	13 (3.6)
Drug overdose	12 (3.3)	13 (3.6)
Musculoskeletal/Connective Tissue	14 (3.9)	12 (3.3)
Respiratory surgery	12 (3.3)	11 (3.0)
Gastrointestinal bleed	10 (2.8)	10 (2.8)
Vascular surgery	7 (1.9)	7 (1.9)
Diabetes mellitus	4 (1.1)	4 (1.1)
Malignancy	3 (0.8)	4 (1.1)
Endocrine/Nutritional	0 (0)	0 (0)
Kidney, Urinary tract, Reproductive	0 (0)	0 (0)

TABLE 5

ADMISSION AND MOST RESPONSIBLE DIAGNOSES

AMONG ICU AND CCU PATIENTS (N = 362)

	Admission Diagnosis Frequency (%)	**Most Responsible Diagnosis Frequency (%)**
CCU Patients*	189 (52.2)	190 (52.5)
ICU Patients*	173 (47.8)	172 (47.5)

* CCU Patients consisted of acute myocardial infarction, cardiovascular non-surgery (CHF, arrhythmias, hyper/hypotension), and unstable angina.

* ICU Patients consisted of the other 14 diagnoses.

Table 6 shows the incidence of thrombocytopenia in the 362 patients with an ICU and CCU admission and most responsible diagnoses. Thrombocytopenia developed more often in patients with an ICU than CCU admission and most responsible diagnosis.

For a variety of reasons, investigators have used different thresholds for thrombocytopenia (see Section 1.2). The data in Table 7 summarize the frequencies of thrombocytopenia that would have been documented in the study patients at different thresholds. Twenty-eight of 362 (7.7%; 95% CI: 5.0% - 10.4%) patients would have met the criterion for thrombocytopenia of at least one platelet count $< 100 \times 10^9$/L. Twenty-seven of these were ICU patients, and the estimated incidence of thrombocytopenia in this subgroup would have been 15.6% (95% CI: 10.2% - 21.0%). Only one CCU patient had at least one platelet count $< 100 \times 10^9$/L and the estimated incidence of thrombocytopenia in this subgroup would have been 0.5% (95% CI: - 0.5% - 1.6%).

3.3 LOGISTIC REGRESSION ANALYSIS

3.3.1 Logistic regression analysis of baseline variables

3.3.1.1 Univariate Analysis: selecting baseline risk indicators for multivariate logistic regression

Data were collected for 24 potential baseline variables on admission to the ICU/CCU. Univariate analyses were performed on the 24 baseline variables (for inclusion into multivatiate logistic regression analysis) and 13 variables were selected for multivariate logistic regression analysis based on a p-value $\leq$ 0.25 (Table 8).

3.3.1.1.1 Collinearity between baseline risk indicators

Collinearity ($r \geq 0.7$) was not observed for any of the pairs among the 13 baseline risk indicators. Therefore, all 13 baseline risk indicators were candidates for multivariate logistic modelling.

TABLE 6

INCIDENCE OF THROMBOCYTOPENIA AMONG PATIENTS WITH ICU AND CCU ADMISSION OR MOST RESPONSIBLE DIAGNOSES

	Thrombocytopenia
CCU Admission Diagnosis (N = 189)	15 (7.9%) (95% CI: 4.1% - 11.7%)
ICU Admission Diagnosis (N = 173)	53 (30.6%) (95% CI: 23.7% - 37.5%)
CCU Most Responsible Diagnosis (N = 190)	17 (8.9%) (95% CI: 4.9% - 12.9%)
ICU Most Responsible Diagnosis (N = 172)	51 (29.7%) (95% CI: 22.9% - 36.5%)

TABLE 7

INCIDENCE OF THROMBOCYTOPENIA BASED ON DIFFERENT CRITERIA AMONG PATIENTS ADMITTED TO THE ICU/CCU

	Entire Study Sample (N = 362)	ICU (N = 172)	CCU (N = 190)
ONE or more Platelet Counts:			
$< 150 \times 10^9$/L	96 (26.5%)	63 (36.6%)	33 (17.4%)
$< 100 \times 10^9$/L	28 (7.7%)	27 (15.7%)	1 (0.5%)
$< 50 \times 10^9$/L	13 (3.6%)	12 (7.0%)	1 (0.5%)
TWO or more Platelet Counts:			
$< 150 \times 10^9$/L	68 (18.8%)	51 (29.7%)	17 (8.9%)
$< 100 \times 10^9$/L	23 (6.4%)	22 (12.8%)	1 (0.5%)
$< 50 \times 10^9$/L	12 (3.3%)	11 (6.4%)	1 (0.5%)

3.3.1.1.2 Linearity of continuous baseline risk indicators

The assumption of linearity in the logit was examined for all 3 continuous baseline variables. For example, admission platelet count was a continuous variable identified as being associated with the development of thrombocytopenia by univariate analysis. In order to determine whether there was a linear relationship between the logit and admission platelet count, 3 design or dummy variables were created based on the quartiles of admission platelet count. These 3 design variables were substituted for admission platelet count, in the model. Results of this fit are summarized in Table 9. In addition to the estimated logistic regression coefficients (β), Table 9 contains the midpoint of each quartile, and the point and interval estimates for the odds ratios calculated from the estimated coefficients. The estimated coefficients and odds ratios in Table 9 indicate that there was a linear trend and this is shown in Figure 6. The Pearson correlation coefficient, r, was 0.999 ($r^2 = 0.99$) ($p = 0.023$).

Investigation of linearity in the logit was also performed for the other two continuous baseline risk indicators, APACHE II score and age. The estimated coefficients and odds ratios indicated that these 2 risk indicators were linear in the logit and were kept as continuous variables.

3.3.1.2 Multivariate baseline model

The 8 risk indicators identified following multivariate logistic regression analysis are shown in order of decreasing odds ratio (Table 10). Sepsis and gastrointestinal admission diagnosis had the two highest odds ratios, respectively. Interestingly, 9 of the 14 (64.3%) patients with a gastrointestinal diagnosis had a surgical procedure performed within 24 hours of their admission to the unit. APACHE II score appeared as one of the 8 risk indicators in the model and is a measure of severity of illness in critically ill patients. A higher score was associated with the development of thrombocytopenia. The 5 admission diagnoses (sepsis, gastrointestinal, GI bleed, musculoskeletal/connective tissue, and respiratory non-surgery) selected as risk indicators in the baseline model were all associated with an increased risk of thrombocytopenia and along with APACHE II score. Admission platelet count and age were associated with a decreased risk of thrombocytopenia for an incremental increase in their value. For example, the beta coefficient for admission platelet count was -0.73, which represents the change in the log odds for an

TABLE 8

CANDIDATE BASELINE VARIABLES SELECTED BY UNIVARIATE ANALYSIS

Baseline Variable	p-value
Acute myocardial infarction admission diagnosis*	< 0.001
Admission platelet count*	0.001
Age*	0.081
Alcohol history	0.007
APACHE II score	< 0.001
Gastrointestinal admission diagnosis[a]	0.002
GI bleed admission diagnosis	0.082
Musculoskeletal/Connective tissue admission diagnosis[b]	0.002
Respiratory non-surgery admission diagnosis[c]	0.020
Sepsis admission diagnosis	0.046
Unstable Angina admission diagnosis*	0.005
Nervous system admission diagnosis	0.130
Surgery within 24 hours of ICU/CCU admission	0.065

* Candidate variables associated with a decreased risk for the development of thrombocytopenia

[a] Gastrointestinal surgery 9; Pancreatitis 2; Gastritis 2; Achlorhydria 1

[b] Trauma 8; Fractures (fall) 4; Back surgery 1; Back pain 1

[c] Respiratory failure 42; COPD 8; PE 6; ARDS 1

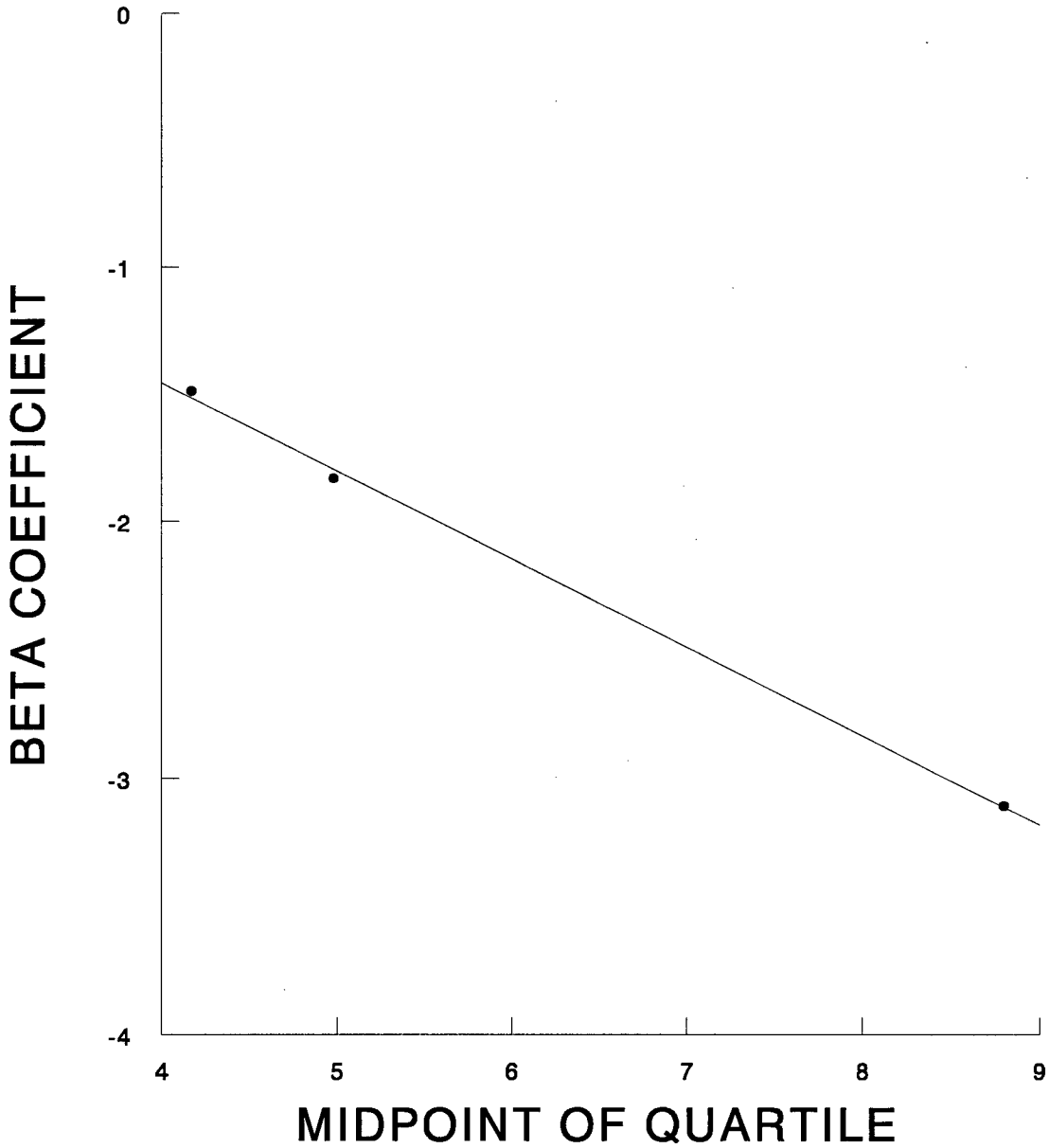
TABLE 9

QUARTILE ANALYSIS OF ADMISSION PLATELET COUNT TO EXAMINE LINEARITY IN THE LOGIT

Quartile	**1**	**2**	**3**	**4**
Range	3.02-3.85	3.86-4.48	4.49-5.47	5.48-12.12
Midpoint	3.44	4.17	4.98	8.80
β	0	-1.4883	-1.8307	-3.1086
Odds Ratio (ψ)	1.0	0.2258	0.1603	0.0449
95% CI	-	0.0927-0.5500	0.0632-0.4064	0.0139-0.1445

Figure 6 **Estimated beta coefficients and midpoints of the quartiles of admission platelet count in assessing linearity in the logit**

Pearson correlation coefficient, r was 0.999 ($r^2 = 0.99$) ($p = 0.023$)



increase of 50 × 10^9/L in the admission platelet count. The estimated odds ratio for an increase of 50 × 10^9/L is 0.48. This indicates that for every increase of 50 × 10^9/L in admission platelet count, the predicted odds ratio of thrombocytopenia is reduced approximately by a half. Similarly, the beta coefficient for age was -0.13 and the odds ratio was 0.88. This represents an approximate reduction of one-tenth in the predicted odds ratio of developing thrombocytopenia for an increase of 5 years in a patient's age.

It is possible that age was serving as a marker for cardiac admission (acute myocardial infarction, unstable angina, or cardiovascular non-surgery) because the CCU patient sample had a higher mean age (66.4 years ± 12.4 years) than the ICU patients (59.7 years ± 17.5 years), and a lower incidence of thrombocytopenia (Table 7) than ICU patients.

To investigate the possibility that age was a marker for CCU admission diagnosis, cardiac admission diagnoses (acute myocardial infarction, cardiovascular non-surgery, and unstable angina) were grouped together as a candidate variable (cardiac admission diagnosis) and multivariate logistic modelling was performed. It is important to note that cardiac diagnosis included acute myocardial infarction, cardiovascular non-surgery, and unstable angina; whereas only acute myocardial infarction and unstable angina had been identified as candidate variables by univariate analysis. Following multivariate logistic regression with cardiac admission diagnosis and the other 11 candidate variables, including age, the same 8 variable model resulted as shown in Table 10. This suggests that age was probably not simply a marker for CCU admission diagnosis, but was providing additional information regarding risk of thrombocytopenia. Thus, age was retained in the model as an independent predicator for the development of thrombocytopenia.

Figure 7 illustrates the probability of developing thrombocytopenia for patients with the mean values of the continuous variables: admission platelet count, APACHE II score, and age, and no other risk indicators; and the probability of developing thrombocytopenia for patients with one of the 8 independent risk indicators identified in the baseline logistic regression model. For the three continuous

TABLE 10

MULTIVARIATE BASELINE MODEL FOR THE

DEVELOPMENT OF THROMBOCYTOPENIA

Variable	Coefficient (β)*	Standard Error**	Wald	Odds Ratio	95% CI OR	p-Value
Sepsis	2.64	0.80	10.81	14.05	2.91-67.86	0.0010
Gastrointestinal Diagnosis	2.03	0.66	9.41	7.61	2.08-27.85	0.0022
GI Bleed	1.91	0.75	6.45	6.73	1.55-29.32	0.0111
Musculoskeletal/ Connective Tissue	1.78	0.66	7.39	5.93	1.64-21.42	0.0066
Respiratory Non-Surgery	0.82	0.41	3.98	2.27	1.01-5.09	0.0047
APACHE II score[a]	0.096	0.018	29.58	1.10	1.06-1.14	< 0.0001
Age[b]	-0.13	0.05	6.57	0.88	0.80-0.97	0.0104
Admission Platelet Count[c]	-0.73	0.16	21.09	0.48	0.35-0.66	< 0.0001
Constant	1.26	0.92	1.89			0.1688

[a] = per 1 unit increase. A change in the log odds β for an increase of 1 unit in the APACHE II score.
[b] = per 5 year increase. A change in the log odds β for an increase of 5 years of age.
[c] = per 50×10^9/L increase. A change in the log odds β for an increase of 50×10^9/L in the admission platelet count.

Regression Equation for the Baseline Model:

logit (thrombocytopenia) = 1.26 + 2.64 (sepsis) + 2.03 (gastrointestinal) + 1.91 (GI Bleed) + 1.78 (musculoskeletal/connective tissue) + 0.82 (respiratory non-surgery) + 0.10 (APACHE II score) - 0.73 (admission platelet count) – 0.13 (Age)

risk indicators (age, admission platelet count, and APACHE II score), the probability of developing thrombocytopenia was also estimated at one standard deviation above the mean.

Table 11 shows some of the logistic regression model statistics for the baseline model. The likelihood is the probability of the observed results given the parameter estimates. Logistic regression uses –2 log-likelihood (-2LL) as a measure of how well the estimated model fits the data. A reasonable model results in a high likelihood of the observed results and hence, a small –2LL. The baseline model resulted in a –2LL of 258.93. The Cox-Snell R^2 (R_c) for the model was 0.222. As mentioned in section 2.2.2.2.9, the Cox-Snell R^2 can reach a maximum of 0.75. The Nagelkerke R^2 (R_N) for the model was 0.36. When the predicted probability of each case was correlated with the observed outcome of thrombocytopenia, the correlation coefficient, r, was 0.53, yielding an r^2 of 0.28.

The Hosmer-Lemeshow Goodness of fit test yielded a value of 7.14, which, based on a chi-square distribution with 8 degrees of freedom, resulted in a p-value of 0.52. Since the Hosmer-Lemeshow Goodness of fit test is based on the null hypothesis that the model is a reasonable fit of the observed data, a p-value > 0.05 results in failure to reject the null hypothesis and indicates that the model is a reasonable fit of the observed data (Hosmer and Lemeshow, 1989; Hosmer and Lemeshow, 1991).

A classification table was used to assess how well the model fit the observed data. Overall, 305 of 362 (84.3%) patients were correctly classified. The baseline model had a sensitivity of 39.7%, meaning 27 of 68 patients who developed thrombocytopenia were correctly classified as developing thrombocytopenia. The model had a specificity of 94.6%, indicating that 278 of 294 patients who did not develop thrombocytopenia were correctly predicted by the model not to have developed thrombocytopenia.

3.3.1.3 Interactions among variables in the baseline model

Possible interactions among the 8 variables in the baseline model were investigated, and the results are shown in Table 12. Interactions with a p-value ≤ 0.05 were deemed statistically significant and were forced into the 8 variable baseline model. Three interactions were statistically significant: admission platelet count by musculoskeletal/connective tissue, APACHE II score by gastrointestinal

Figure 7: Effect of the individual risk indicators in the baseline model on the predicted probability of developing thrombocytopenia. Dark coloured bars indicate the predicted probability of thrombocytopenia in patients whose admission platelet count, APACHE II score, and age are equal to the respective sample mean values and who have no other risk indicators. Light coloured bars indicate the predicted probability of thrombocytopenia in patients with one of the individual dichotomous variables or whose value for one of the three continuous variables is one standard deviation above the mean value on admission of the study sample.

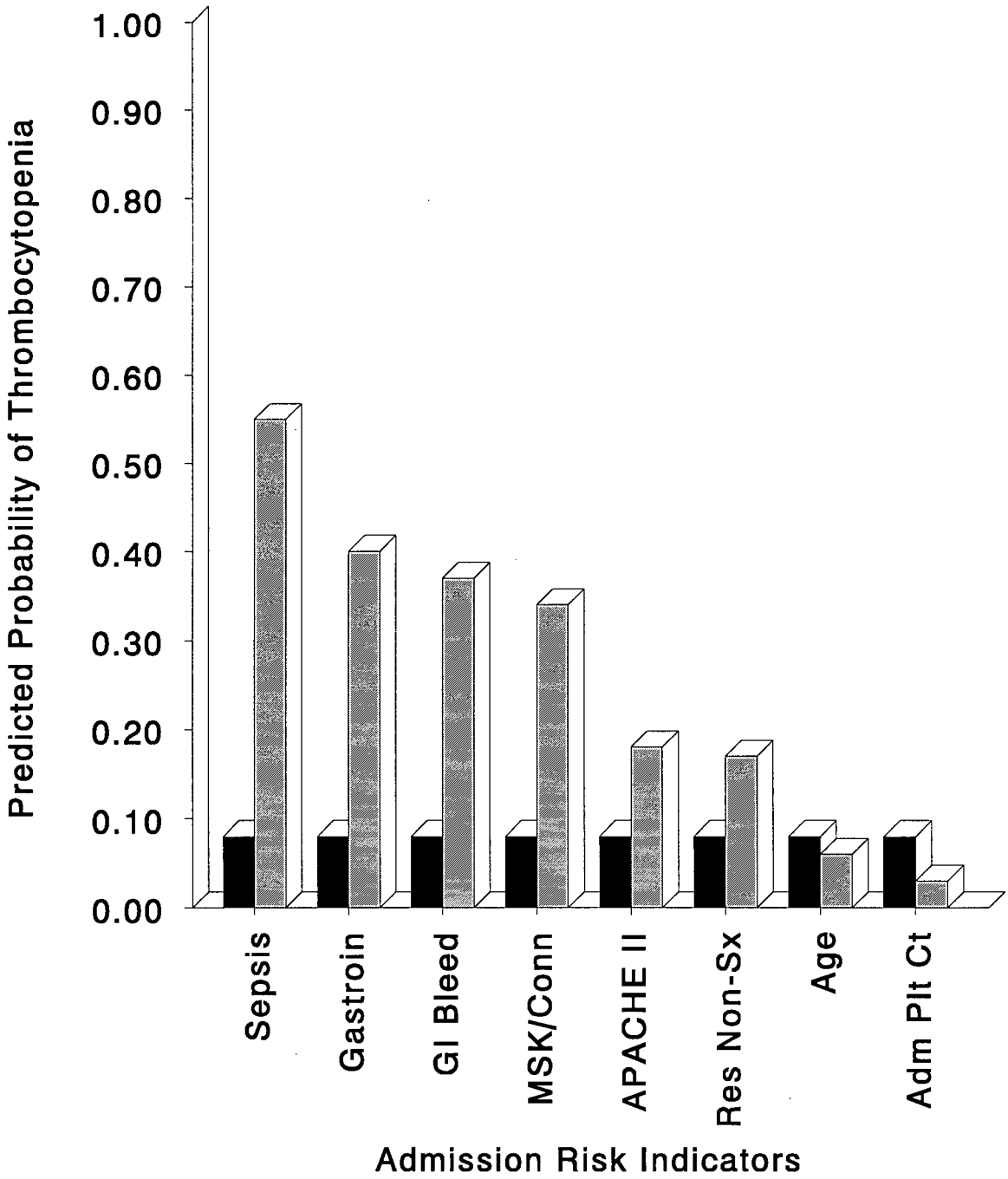


TABLE 11

BASELINE MODEL LOGISTIC REGRESSION STATISTICS

Model Statistics	
-2 Log-Likelihood	258.93
Cox-Snell R^2	0.22
Nagelkerke R^2	0.36
Observed vs. Predicted Pearson's R^2	0.28
Hosmer-Lemeshow Goodness-of-fit	$p = 0.52$
Overall Correct Classification	84.3%
Sensitivity	39.7%
Specificity	94.6%

diagnosis, and APACHE II score by GI bleed. When each of these interactions was individually entered into the multivariate model with the 8 variables, none appeared to enhance the model. Therefore, no interaction term was added to the baseline model.

3.3.1.4 Evaluation of the baseline model

Regression diagnostic analyses were performed to identify patients whose observed outcome deviated from the expected or predicted outcome. Analyses of the studentized residuals, Cook's distance, difference in beta coefficients for each of the 8 baseline model variables, and leverage versus the predicted probability were done in order to identify cases that were outliers. Scatter plots for studentized residual and predicted probability (Figure 8), leverage and predicted probability (Figure 9), and Cook's Distance and predicted probability (Figure 10) were generated. In addition, a scatter plot of the studentized residual and admission platelet count was done, and it demonstrated that all the cases, except one (patient # 389) were within ± 3 standard deviations.

The scatter plot of the studentized residual and the predicted probability (Figure 8) indicated that all, except one (patient # 389) of the studentized residuals are within ± 3 standard deviations. The data from this patient were determined to have been entered correctly into the SPSS® database.

Patient # 389 was a 62 year old female admitted to the ICU/CCU with chest pain after 11 days on the hospital ward. She had an admission APACHE II score of 9 and had a Swan-Ganz catheter inserted upon admission to the unit. She experienced a hemorrhage on day 3, and developed thrombocytopenia on day 4 of her ICU/CCU stay. This patient was identified as an outlier because she developed thrombocytopenia, but had a predicted probability of developing thrombocytopenia of only 0.002. Since she met the clinical criteria for admission to the unit (suspected unstable angina requiring intravenous nitroglycerin and hemodynamic monitoring), she was not excluded from the analysis even though her studentized residual was greater than 3 standard deviations from the mean.

Leverage values were used for detecting observations that had a large impact on the predicted probabilities. A scatter plot of leverage and the predicted probability is shown in Figure 9. No patient

TABLE 12

INTERACTIONS AMONG VARIABLES IN THE BASELINE MODEL

Interaction	-2 Log-Likelihood	G	Df	p-value
Main Effects	258.931			
Admission platelet count * Age	252.757	0.175	1	0.68
Admission platelet count * APACHE II	256.923	2.009	1	0.16
Admission platelet count * Gastrointestinal	258.616	0.315	1	0.57
Admission platelet count * GI Bleed	257.831	1.100	1	0.29
Admission platelet count * Musculoskeletal	**244.426**	**14.506**	**1**	**< 0.01**
Admission platelet count * Respiratory no surgery	258.930	0.001	1	0.98
Admission platelet count * Sepsis	257.138	1.793	1	0.18
Age * APACHE II	258.789	0.142	1	0.71
Age * Gastrointestinal	258.709	0.222	1	0.64
Age * GI Bleed	258.132	0.799	1	0.37
Age * Musculoskeletal	258.820	0.112	1	0.74
Age * Respiratory no surgery	257.976	0.955	1	0.33
Age * Sepsis	257.167	1.764	1	0.18
APACHE II * Gastrointestinal	**255.157**	**3.775**	**1**	**0.05**
APACHE II * GI Bleed	**245.740**	**13.192**	**1**	**< 0.01**
APACHE II * Musculoskeletal	258.760	0.171	1	0.68
APACHE II * Respiratory no surgery	256.872	2.060	1	0.15
APACHE II * Sepsis	258.724	0.207	1	0.65

had large leverage values, but data from patients identified as having higher leverage values were checked for correct entry into the database.

Cook's distance and difference in betas were plotted against the predicted probabilities in order to examine the influence of each case. Figure 10 shows a scatter plot of Cook's distance and predicted probabilities of thrombocytopenia. The one extreme case (patient # 389) was checked for proper data entry into the SPSS® database.

3.3.1.5 Receiver operating characteristic (ROC) curve for the baseline model

As shown in Figure 11, a ROC curve was generated from the predicted probabilities and observed outcomes. Based on the magnitude of the area under the ROC curve, good association was found between predicted and observed outcome. The area under the curve, or c index, was 0.847 (95% CI: 0.796 – 0.898).

3.3.2 Logistic regression analysis of ICU/CCU variables

ICU/CCU variables included baseline risk indicators and risk indicators patients were exposed to on the unit up to the development of thrombocytopenia, or discharge or death if thrombocytopenia did not develop.

3.3.2.1 Univariate analysis: selecting ICU/CCU risk indicators for multivariate logistic regression

Data were collected for 126 risk indicators identified *a priori*. The 126 variables included baseline risk indicators and those patients were exposed to in the ICU/CCU up to the first platelet count < 150×10^9/L for those who developed thrombocytopenia and to discharge or death for those who did not develop thrombocytopenia. Of these 126 risk indicators, 55 were not subjected to univariate analysis because patients either were not exposed to them, or had an exposure frequency of less than 5%. Hence, 71 risk indicators were analysed by univariate analysis, and the resulting measures of association are summarized in Appendix 4. Variables associated with thrombocytopenia with a value of $p \leq 0.25$ were considered for inclusion in subsequent multivariate analysis.

Figure 8 **Scatter plot of Studentized Residuals and Predicted Probability for the Baseline Model**

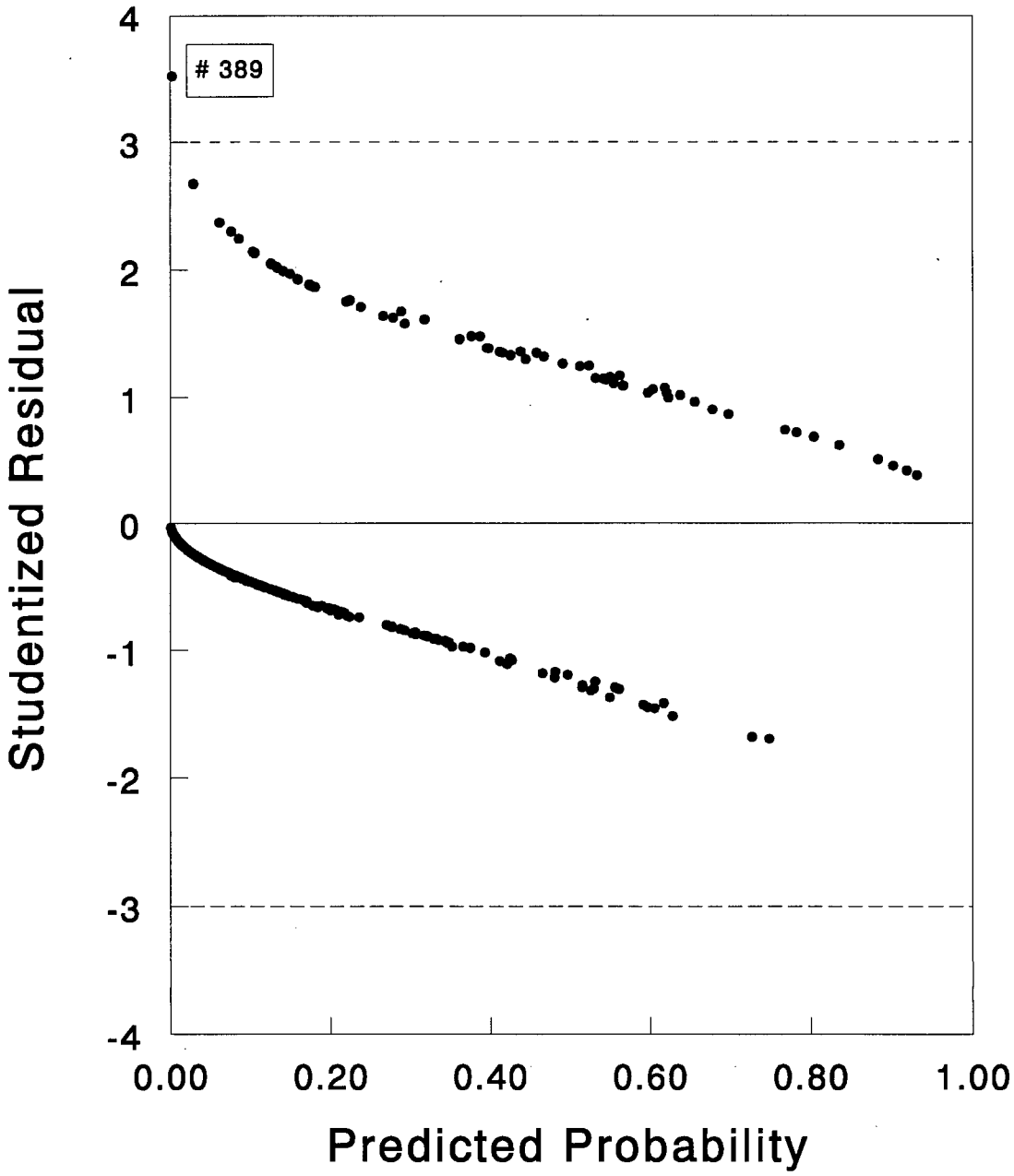


Figure 9 **Scatter plot of Leverage and Predicted Probability for the Baseline Model**

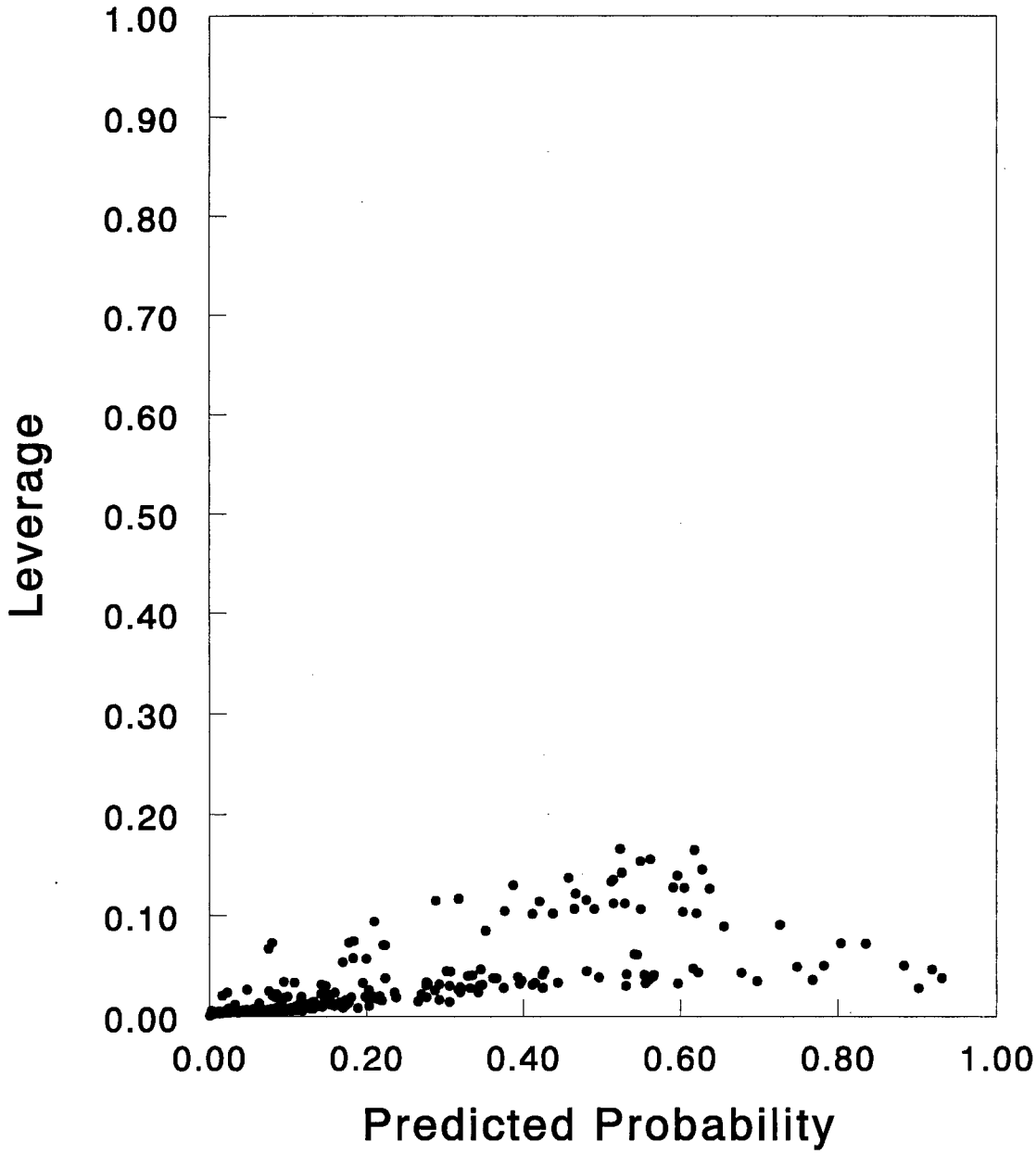
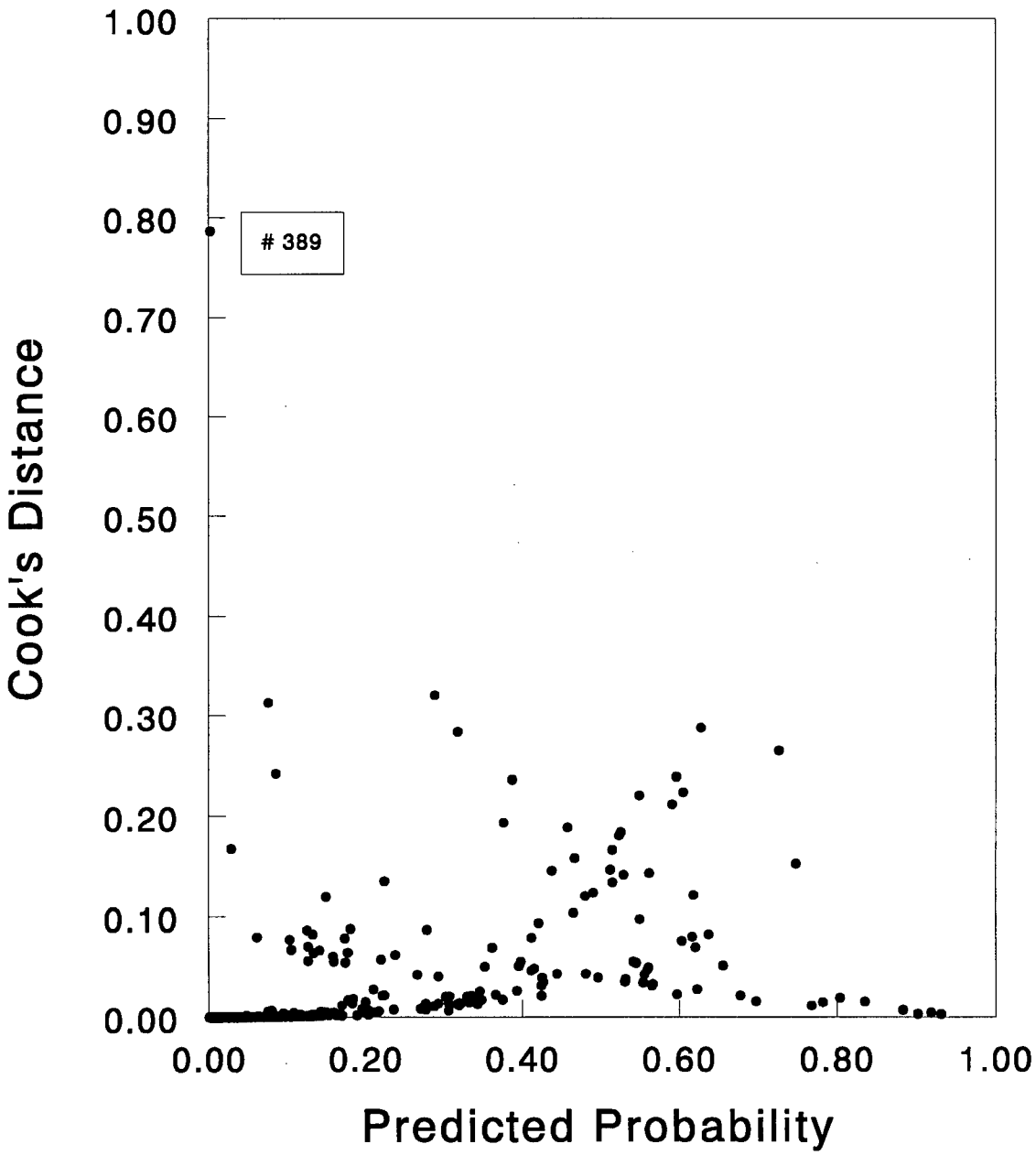


Figure 10 **Scatter plot of Cook's Distance and Predicted Probability**



Demographic patient characteristics identified by univariate analysis as candidate variables were the patient's age, APACHE II score, APS, and history of alcohol use.

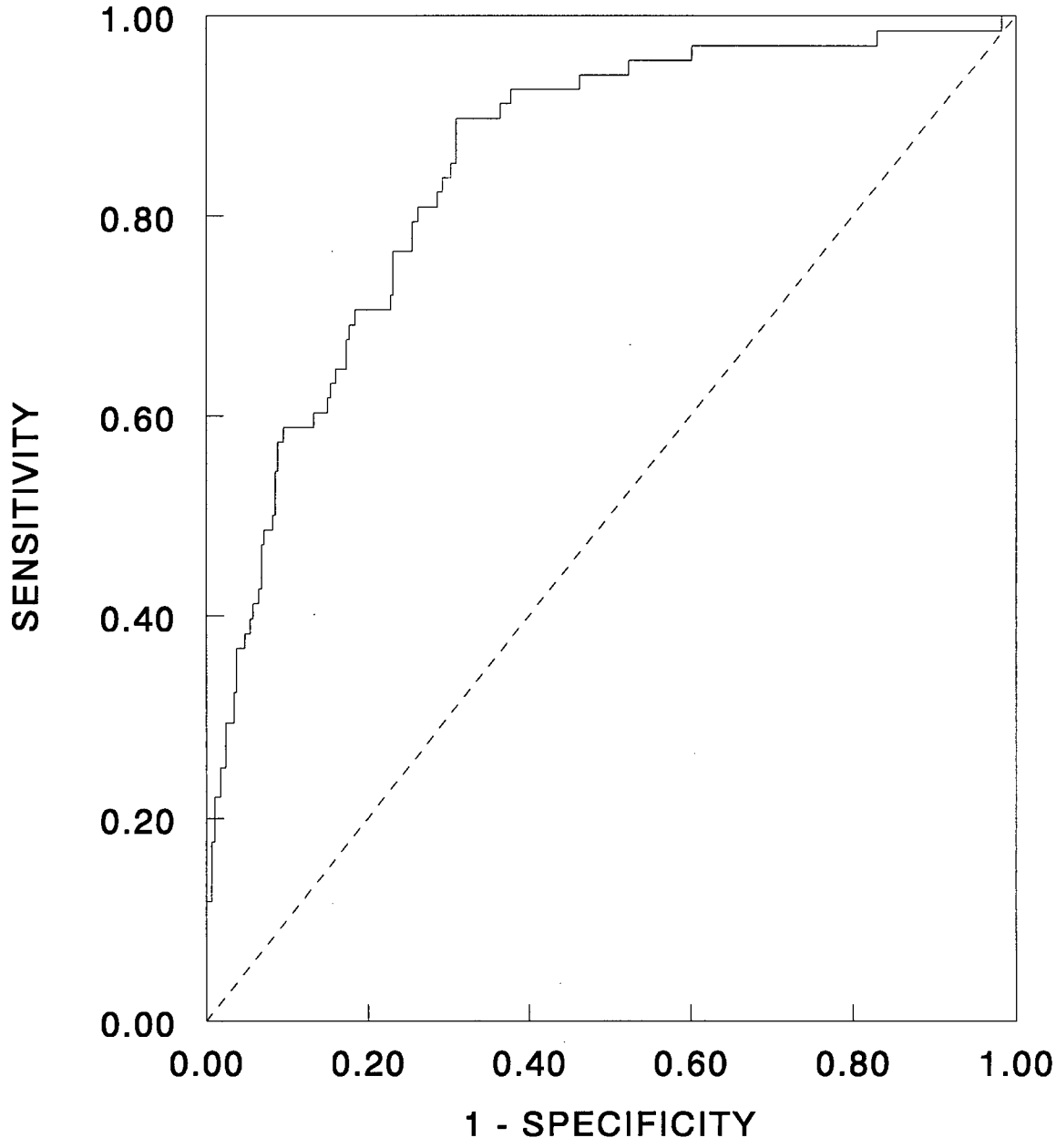
Many medications were associated with thrombocytopenia by univariate analysis. These included acetylsalicylic acid (ASA), cefazolin, ceftizoxime, dopamine, imipenem, ipratropium bromide, norepinephrine, ranitidine, salbutamol, and tinzaparin. Two medications, cotrimoxazole and vancomycin, met the criterion, but were not selected for multivariate modelling. Cotrimoxazole had a zero cell, meaning no patients who received cotrimoxazole developed thrombocytopenia, and only 3 (0.8%) patients were exposed to vancomycin. Interestingly, certain medications, such as quinine and quinidine, which have been reported to be associated with thrombocytopenia, were not selected as candidate variables for univariate analysis because of low patient exposure. Also, heparin, when included as a dichotomous variable, was not identified as being associated with the development of thrombocytopenia by univariate analysis.

In addition, because of low exposure of patients to many of the medications identified *a priori*, five medication classes were developed based on similarities in chemical structure and pharmacological action. The results of the univariate analyses involving these dependent variable thrombocytopenia and the 5 classes of medications are shown in Appendix 4, and indicated that inotropes, cephalosporins, and H_2-antagonists were associated with thrombocytopenia. Candidate medications were selected once, either as an individual medication or as one of the 3 classes (inotropes, cephalosporins, H_2-antagonists). For example, cefazolin, ceftizoxime, dopamine, norepinephrine, and ranitidine were not selected as individual medications for multivariate analysis because they were categorized into one of the 3 medication classes. Only, acetylsalicylic acid, imipenem, ipratropium bromide, salbutamol, and tinzaparin were selected individually as candidates for multivariate analysis.

To further explore the role of heparin in the occurrence of thrombocytopenia, univariate analysis was performed on patients receiving different daily doses of heparin. Heparin (dose/day), as a continuous variable, was found to be associated with thrombocytopenia following univariate analysis. When heparin was analyzed as a dichotomous variable, it was not identified as a candidate variable. Because high dose

Figure 11 **Receiver operating characteristic curve for the baseline model**

The dotted line represents a c index of 0.5, which indicates the model has no discrimination ability. [c index = 0.847]



heparin therapy tends to be administered to patients with a cardiac diagnosis, heparin therapy was also investigated by univariate analysis as a dichotomous variable in 3 different categories: low dose (< 1000 units/day), medium dose (1000 – 16,000 units/day), and high dose (< 16,000 units/day). Medium dose heparin was found to be positively associated with thrombocytopenia; whereas high dose heparin was found to be negatively associated with thrombocytopenia by univariate analysis. Only heparin as a continuous variable was selected as a candidate variable.

The following most responsible diagnoses were selected as candidate variables by univariate analysis: acute myocardial infarction, gastrointestinal disorders, gastrointestinal (GI) bleed, infection, musculoskeletal and connective tissue disorders, nervous system disorders, non-surgery respiratory disorders, sepsis, and unstable angina.

Among the procedures identified *a priori*, variables selected as candidates for multivariate analysis were: surgeries performed within the previous 24 hours before admission to the ICU/CCU, swan ganz (pulmonary artery) catheter insertion, packed red blood cell transfusions, fresh frozen plasma transfusions, and mechanical ventilation. Interestingly, surgeries performed while the patient was in the ICU/CCU were not associated with thrombocytopenia by univariate analysis.

Hepatic dysfunction, but not renal dysfunction, was selected as a candidate variable following univariate analysis.

Admission platelet count was the only laboratory value associated with the development of thrombocytopenia by univariate analysis and selected as a candidate variable.

Of the 71 variables subjected to univariate analysis, 31 were initially selected as candidates for multivariate logistic regression. The number of candidate variables was further reduced by categorizing 5 medications, dopamine, cefazolin, ceftizoxime, norepinephrine, and ranitidine, into 3 medication classes, inotropes, cephalosporins, and H_2-antagonists, and adding them to the list of candidate variables. In addition, tinzaparin, which was administered to 16 (4.4%) patients, was eliminated as a candidate variable because it was prescribed by one physician for conditions that were not documented indications for the drug at that time. This further reduced the list of candidate variables to 28.

3.3.2.1.1 Collinearity between ICU/CCU risk indicators

Collinearity was assessed among candidate variables to identify those that had a high degree of association with one another. Collinearity was apparent in 3 pairs of variables, as shown in Table 13. Acute Physiology score (APS) and APACHE II score demonstrated the highest association (r = 0.967). This meant that both variables conveyed essentially the same information about the variation in thrombocytopenia. Since the APS is a component of the APACHE II score and the APACHE II is a well recognized instrument used to assess disease severity, it was selected as a candidate for multivariate analysis. Salbutamol was selected for use in multivariate analysis over ipratropium bromide because of its greater frequency of use. Similarly, APACHE II score was selected over mechanical ventilation because the APACHE II score was performed on all patients and is a better measure of severity of illness than mechanical ventilation. Therefore, 3 variables were excluded because of collinearity with other candidate variables, leaving 25 variables as candidates for multivariate analysis (Table 14).

3.3.2.1.2 Linearity of continuous ICU/CCU risk indicators

The assumption of linearity in the logit was examined for all continuous variables as previously demonstrated in Section 3.3.1.1.2. Linearity in the logit was performed for admission platelet count and heparin dose/day. The estimated coefficients and odds ratios indicated that these 2 risk indicators were linear in the logit and were kept as continuous variables.

3.3.2.2 Multivariate ICU/CCU model

The 25 candidate variables were subjected to backward stepwise multivariate logistic regression analysis, and the results are shown in Table 15, in decreasing order of the odds ratio. Nine variables were identified as being independently associated with thrombocytopenia: fresh frozen plasma (FFP) transfusions, sepsis, musculoskeletal and connective tissue diagnosis, swan ganz (pulmonary artery) catheter insertion, gastrointestinal diagnosis, packed red blood cell (PRBC) transfusions, respiratory non-surgery diagnosis, ASA, and admission platelet count. Fresh frozen plasma transfusions and sepsis had the two highest odds ratios, respectively. Two of the independent risk indicators, FFP and PRBC,

TABLE 13

COLLINEARITY AMONG CANDIDATE VARIABLES

Variables Associated with Each Other	Correlation Coefficient (r)
APS/APACHE II score	0.967
Salbutamol/Ipratropium Bromide	0.897
APACHE II score/Mechanical Ventilation	0.786
APS/ Mechanical Ventilation	0.801

TABLE 14

CANDIDATE ICU/CCU VARIABLES SELECTED BY UNIVARIATE ANALYSIS

Candidate Variables	p-value
Acute myocardial infarction most responsible diagnosis*	0.002
Admission platelet count*	< 0.001
Age*	0.081
Alcohol history	0.007
APACHE II score	< 0.001
ASA*	< 0.001
Fresh frozen plasma transfusions	< 0.001
Gastrointestinal most responsible diagnosis	0.032
GI Bleed most responsible diagnosis	0.082
Heparin dose/day*	0.001
Imipenem	< 0.001
Infection*	0.163
Liver dysfunction	0.005
Musculoskeletal/Connective most responsible diagnosis	< 0.001
Respiratory non-surgery most responsible diagnosis	0.006
Salbutamol	0.001
Sepsis most responsible diagnosis	0.001
Surgery within 24 hours of ICU/CCU admission	0.065
Packed red blood cell transfusions	< 0.001
Unstable angina most responsible diagnosis*	0.010
Medication class inotropes	< 0.001
Medication class cephalosporins	0.010

* Candidate variables associated with a decreased risk for the development of thrombocytopenia

TABLE 14 CONTINUED

CANDIDATE ICU/CCU VARIABLES SELECTED BY UNIVARIATE ANALYSIS

Candidate Variables	p-value
Medication class H_2-antagonists	0.001
Nervous system most responsible diagnosis	0.098
Swan Ganz catheter	< 0.001

appeared to indicate that bleeding episodes were associated with the development of thrombocytopenia. The 4 most responsible diagnoses (sepsis, musculoskeletal and connective tissue, gastrointestinal diagnosis, and respiratory non-surgery) selected as risk indicators in the ICU/CCU model were all associated with an increased risk of thrombocytopenia. Interestingly, APACHE II score was not identified as an independent risk indicator for the development of thrombocytopenia in this model. Admission platelet count and ASA were associated with a decreased risk of thrombocytopenia. For example, the beta coefficient for ASA was (–0.80). and the estimated odds ratio was (0.44). This indicates that a patient exposed to ASA had an estimated odds of developing thrombocytopenia that is approximately two-fifths that of a patient not given ASA. The complete printout of the logistic regression analysis is shown in Appendix 4.

Figure 12 illustrates the probability of developing thrombocytopenia for patients with the mean value of the admission platelet count and no other risk indicators; and the probability of developing thrombocytopenia for patients with each of the other 9 independent risk indicators identified in the ICU/CCU model (in the presence of the mean admission platelet count). For the continuous risk indicator, admission platelet count, the probability of developing thrombocytopenia was estimated at one standard deviation above the mean.

It is possible that ASA appeared to be protective because more CCU patients received this medication (84.9.% vs. 15.1% of ICU patients), and fewer of them developed thrombocytopenia (Table 7). To investigate the possibility that ASA was a marker for CCU most responsible diagnosis, CCU was entered into the model as a separate group variable. Acute myocardial infarction (AMI) and unstable angina (UA) were removed, while the individual ICU diagnoses were left in the model. Two CCU group variables were generated and entered into the model separately; these consisted of: 1) AMI, cardiovascular non-surgery, and UA and 2) AMI and UA. The reason for generating two different groups of CCU diagnoses was due to cardiovascular non-surgery not being identified as a candidate variable by univariate analysis (it was not one of the 25 candidate variables). ASA was initially included with each of the two CCU variables and then excluded as a candidate variable with each CCU group variable. Hence, 4 new models were generated. When ASA was included with each of the 2 CCU

diagnoses groups, the same 9 variable model resulted, as shown in Table 15. ASA appeared in the model, but neither of the 2 CCU most responsible diagnosis groups appeared. When ASA was not included with each of the CCU diagnoses groups, a 10 variable model resulted, again without either of the 2 CCU diagnosis groups. This suggests that ASA was providing more information than that of a marker for CCU diagnosis.

Table 16 demonstrates some of the logistic regression model statistics for the ICU/CCU model. This model resulted in a –2 LL of 226.190 and a Nagelkerke R^2 (R_N) of 0.47. The degree of association between the predicted probability and the observed outcome, as defined by the Pearson correlation coefficient, r, was 0.610 (r^2 of 0.37) and indicates a reasonable degree of association between the predicted probabilities and the observed outcomes (Mittlbock and Schemper, 1996). The Hosmer-Lemeshow goodness-of-fit test resulted in a Chi-square value of 12.09 ($p = 0.15$). This suggests that the ICU/CCU model is a reasonable fit of the observed data (Hosmer-Lemeshow, 1989; Hosmer-Lemeshow, 1991).

The final ICU/CCU model had a sensitivity of 51.5%, meaning 35 of 68 patients who developed thrombocytopenia were correctly classified by the model as developing thrombocytopenia. This model had a specificity of 95.6%, indicating that 281 of 294 patients who did not develop thrombocytopenia were correctly predicted by the model as not having developed thrombocytopenia.

There were two variables retained in the model (respiratory non-surgery most responsible diagnosis and packed red blood cell (PRBC) transfusions), each with a p-value > 0.05 (Table 15). To evaluate their contribution, these two variables were excluded from the model, and the resulting 7 variable model is shown in Table 17. This model contained one variable, gastrointestinal most responsible diagnosis, with a p-value > 0.05. The –2LL was larger than the 9 variable model (233.22 versus 226.19) and the odds ratios and 95% CI for the odds ratios were higher and wider, respectively. In addition, this 7 variable model resulted in a slight decrease in the correct classification and sensitivity compared to the 9 variable model (87.0% vs. 87.3% and 50.0% vs. 51.5%). Thus, exclusion of respiratory non-surgery most responsible diagnosis and PRBC transfusions did not enhance the model and therefore, these two variables were kept in the ICU/CCU model.

TABLE 15

MULTIVARIATE ICU/CCU MODEL FOR THE DEVELOPMENT OF THROMBOCYTOPENIA

Variable	Coefficient (β)*	Standard Error**	Wald	Odds Ratio	95% CI OR	p-Value
FFP Transfusion	3.00	1.17	6.55	20.04	2.02-199.16	0.0105
Sepsis	2.71	0.81	11.10	15.08	3.06-74.39	0.0009
Musculoskeletal/ Connective Tissue	2.25	0.66	11.58	9.48	2.60-34.60	0.0007
Swan Ganz	2.12	0.39	29.93	8.37	3.91-17.91	< 0.0001
Gastrointestinal	1.41	0.70	4.11	4.10	1.05-16.03	0.0427
PRBC Transfusion	0.92	0.50	3.32	2.50	0.93-6.69	0.0685
Respiratory Non-Surgery	0.84	0.46	3.33	2.32	0.94-5.73	0.0679
ASA	-0.80	0.38	4.36	0.44	0.21-0.95	0.0368
Admission Platelet Count[a]	-0.85	0.19	20.99	0.43	0.30-0.61	< 0.0001
Constant	1.41	0.79	3.14			0.0764

* estimated slope of the regression line

** standard error of the coefficient beta

[a] = per 50×10^9/L increase. A change in the log odds β for an increase of 50×10^9/L in the admission platelet count.

Regression Equation for the ICU/CCU Model:

logit (thrombocytopenia) = 1.41 + 3.00 (FFP transfusion) + 2.71 (sepsis) + 2.25 (musculoskeletal/connective tissue) + 2.12 (swan ganz) + 1.41 (gastrointestinal) + 0.92 (PRBC transfusion) + 0.84 (respiratory non-surgery) - 0.80 (ASA) - 0.85 (admission platelet count)

Figure 12: Effect of the individual risk indicators in the ICU/CCU model on the predicted probability of developing thrombocytopenia. Dark coloured bars indicate the predicted probability of thrombocytopenia in patients whose admission platelet count is equal to the sample mean value and who have no other risk indicators. Light coloured bars indicate the predicted probability of thrombocytopenia in patients with one of the individual dichotomous variables, or whose value for admission platelet count is one standard deviation above the mean admission platelet count

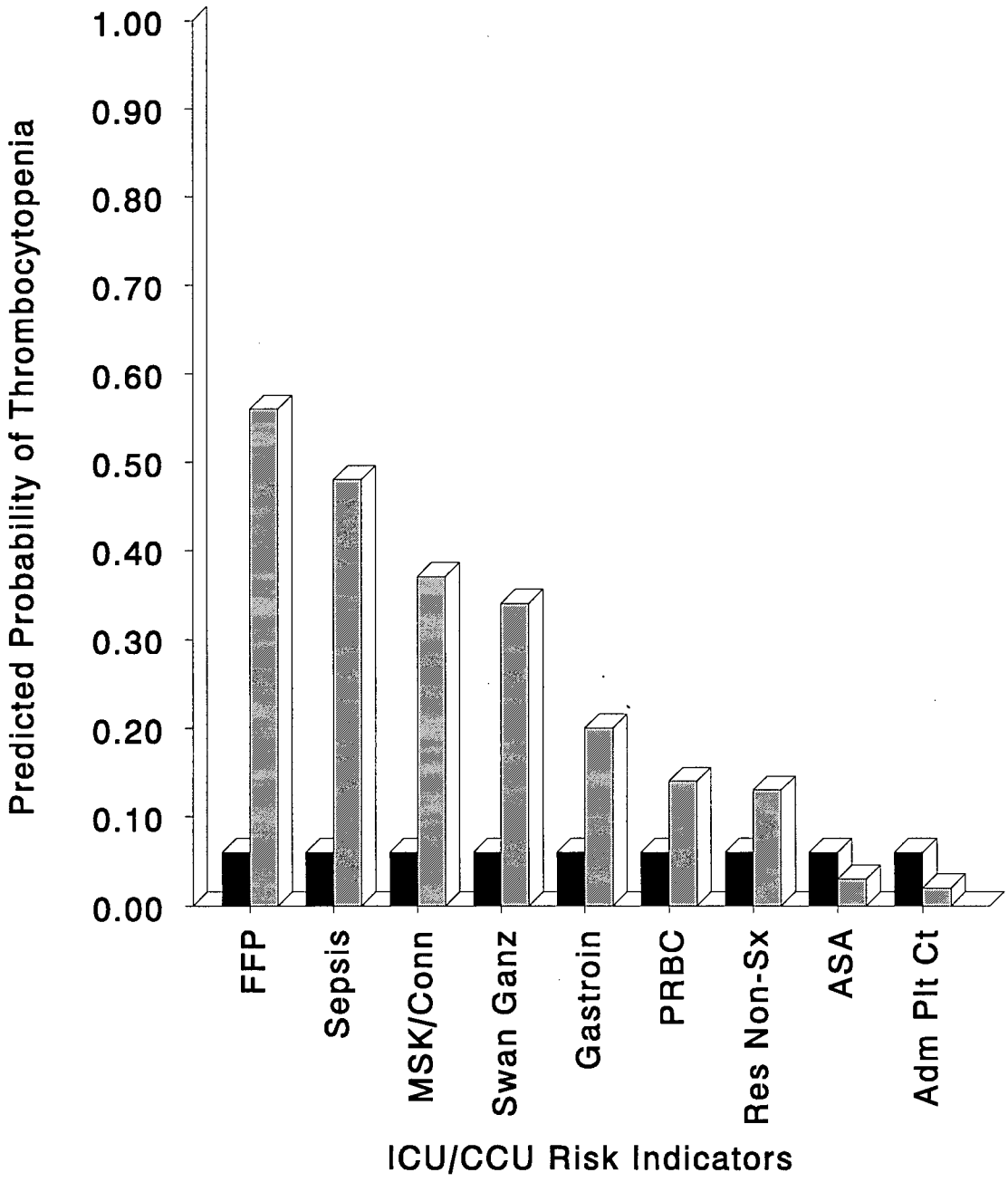


TABLE 16

ICU/CCU MODEL LOGISTIC REGRESSION STATISTICS

Model Statistics	
-2 Log-Likelihood	226.19
Cox-Snell R^2	0.29
Nagelkerke R^2	0.47
Observed vs. Predicted Pearson's R^2	0.37
Hosmer-Lemeshow Goodness-of-fit	$p = 0.15$
Overall Correct Classification	87.3%
Sensitivity	51.5%
Specificity	95.6%

The 9 variable ICU/CCU model was investigated further by generating two 8 variable models by excluding either respiratory most responsible diagnosis or PRBC transfusions. There was no marked change in the resulting two 8 variable models and each had a higher –2LL, wider 95% CI around the odds ratios, and lower sensitivity. In addition, a simple sensitivity analysis was performed to determine the effect of these 2 variables on the predicted probability of developing thrombocytopenia (Table 18). On the basis of the above analyses, it was decided that the 9 variable model, including respiratory non-surgery and PRBC transfusion, was the most reasonable fit to the data. It is also plausible that both respiratory non-surgery and PRBC transfusions are biologically and clinically related to thrombocytopenia, and thus, these risk indicators were retained in the final 9 variable model.

3.3.2.3 Heparin forced into the ICU/CCU model

To investigate whether heparin should be included as an independent risk indicator in the ICU/CCU model, it was forced into the 9 variable ICU/CCU model as a dichotomous variable (present or absent); or administered or not at a low, medium, or high dose; and as a continuous variable (heparin dose/day) (see Section 3.3.2.1). In none of these cases did heparin enhance the multivariate ICU/CCU model (data not shown).

3.3.2.4 Interactions among variables in the ICU/CCU model

Among the 9 variables in the ICU/CCU model, a total of 36 possible interactions were screened (Table 19). There were three interactions (highlighted in bold) that were statistically significant. When two of these interactions, admission platelet count by musculoskeletal/connective tissue most responsible diagnosis and sepsis by PRBC transfusions were individually entered into the 9 variable multivariate model, they did not appear to enhance the model. Therefore, neither of these 2 interactions was added to the ICU/CCU model. The admission platelet count by sepsis interaction was also not added to the model, even though it was statistically significant ($p = 0.003$) when entered into the 9 variable multivariate

TABLE 17

MULTIVARIATE ICU/CCU MODEL EXCLUDING RESPIRATORY NON-SURGERY MOST RESPONSIBLE DIAGNOSIS AND PACKED RED BLOOD CELL TRANSFUSIONS

Variable	Coefficient (β)*	Standard Error**	Wald	Odds Ratio	95% CI OR	p-Value
FFP Transfusion	3.76	1.12	11.31	42.89	4.80-383.35	0.0008
Sepsis	2.46	0.79	9.71	11.66	2.49-54.62	0.0018
Musculoskeletal/ Connective Tissue	2.14	0.65	10.87	8.46	2.38-30.08	0.0010
Swan Ganz	2.32	0.38	37.75	10.22	4.87-21.46	< 0.0001
Gastrointestinal	1.21	0.69	3.06	3.36	0.86-13.07	0.0804
ASA	-0.95	0.37	6.46	0.39	0.19-0.80	0.0110
Admission Platelet Count[a]	-0.78	0.18	19.71	0.46	0.32-0.64	< 0.0001
Constant	1.41	0.78	3.31			0.0686

* estimated slope of the regression line

** standard error of the coefficient beta

[a] = per 50×10^9/L increase. A change in the log odds β for an increase of 50×10^9/L in the admission platelet count.

TABLE 18

PREDICTED PROBABILITY OF THROMBOCYTOPENIA WITH AND WITHOUT RESPIRATORY NON-SURGERY MOST RESPONSIBLE DIAGNOSIS OR PRBC TRANSFUSIONS IN THE ICU/CCU MODEL

Different scenarios	logit (P/1-P)	P (probability)*
Gastrointestinal diagnosis with swan ganz with PRBC Transfusion	2.46	0.92
Gastrointestinal diagnosis with swan ganz without PRBC Transfusion	1.54	0.82
Respiratory diagnosis with swan ganz with PRBC Transfusion	1.89	0.87
Respiratory diagnosis with swan ganz without PRBC Transfusion	0.97	0.73

* P = predicted probability of developing thrombocytopenia

TABLE 19

INTERACTIONS AMONG VARIABLES IN THE ICU/CCU MODEL

Interaction	-2 Log-Likelihood	G	Df	p-value
Main Effects	226.190			
Admission platelet count * ASA	225.376	0.814	1	0.37
Admission platelet count * FFP Transfusion	225.243	0.947	1	0.33
Admission platelet count * Gastrointestinal	226.131	0.059	1	0.81
Admission platelet count * Musculoskeletal	**222.463**	**3.727**	**1**	**0.05**
Admission platelet count * Respiratory non-surgery	226.027	0.161	1	0.69
Admission platelet count * Sepsis	**218.038**	**8.152**	**1**	**< 0.01**
Admission platelet count * PRBC Transfusion	225.966	0.224	1	0.64
Admission platelet count * Swan Ganz	223.895	2.295	1	0.13
ASA * Gastrointestinal	225.152	1.038	1	0.31
ASA * Musculoskeletal	225.534	0.656	1	0.42
ASA * Respiratory non-surgery	225.886	0.303	1	0.58
ASA * Sepsis	224.898	1.292	1	0.26
ASA * PRBC Transfusion	226.149	0.041	1	0.84
ASA * Swan Ganz	224.506	1.684	1	0.19
FFP Transfusion * Gastrointestinal	226.123	0.067	1	0.80
FFP Transfusion * Respiratory non-surgery	224.963	1.227	1	0.27
FFP Transfusion * PRBC Transfusion	226.123	0.067	1	0.80
FFP Transfusion * Swan Ganz	224.154	2.036	1	0.15
Gastrointestinal * PRBC Transfusion	225.045	1.145	1	0.28
Gastrointestinal * Swan Ganz	225.179	1.011	1	0.31
Musculoskeletal * PRBC Transfusion	225.654	0.536	1	0.46

TABLE 19 CONTINUED

INTERACTIONS AMONG VARIABLES IN THE ICU/CCU MODEL

Interaction	-2 Log-Likelihood	G	Df	p-value
Musculoskeletal * Swan Ganz	225.385	0.805	1	0.37
Respiratory non-surgery * PRBC Transfusion	226.189	0.001	1	0.98
Respiratory non-surgery * Swan Ganz	226.059	0.131	1	0.72
Sepsis * PRBC Transfusion	**221.901**	**4.289**	**1**	**0.04**
Sepsis * Swan Ganz	226.154	0.036	1	0.85
PRBC Transfusion * Swan Ganz	223.317	2.873	1	0.09

model. This interaction was not included because it did not result in a major improvement or enhancement in the ICU/CCU model, and the sensitivity decreased slightly from 51.5% without the interaction term to 50.0% with the interaction term. The Hosmer-Lemeshow goodness-of-fit test statistic was also lower. In addition, the occurrence of this interaction term likely reflects changes in a few patients, and there is no clear physiologic reason for retaining this term in the model.

In addition, interactions between heparin and the 9 variables in the ICU/CCU model were investigated; however, none of these were associated with the development of thrombocytopenia.

3.3.2.5 Evaluation of the ICU/CCU model

Regression diagnostic analyses were performed on the 9 variable ICU/CCU model to confirm that patient data were coded and entered correctly and to identify patients whose observed outcome digressed from the predicted outcome. As indicated in Section 3.2.1.4, analyses of the studentized residual, Cook's distance, difference in the beta coefficients for each of the 9 ICU/CCU variables, and leverage and the predicted probability were performed in order to identify individual patients who were outliers. Scatter plots were constructed for studentized residual and predicted probability (Figure 13), leverage and predicted probability (Figure 14), and Cook's Distance and predicted probability (Figure 15).

The scatter plot of the studentized residual and the predicted probability (Figure 13) illustrates that only one patient (# 389) had a studentized residual above 3 standard deviations. As mentioned in Section 3.2.1.4, the data for this patient were correctly entered. This patient developed thrombocytopenia, but had a predicted probability of developing thrombocytopenia during the ICU/CCU stay of 0.005.

As indicated earlier, no patient had high leverage values. There were two extreme cases (patients #389 and #452) identified in the Cook's distance versus predicted probability plot (Figure 15). Examination of the database confirmed that data for these patients were accurate and correctly entered.

3.3.2.5 ROC curve for the ICU/CCU model

Figure 16 illustrates the ROC curve for the ICU/CCU model. The area under the ROC curve or c index was 0.891 (95% CI: 0.851 – 0.932) indicating good association between the predicted probability of developing thrombocytopenia and the actual observed cases of thrombocytopenia.

3.4 EXPLORATORY LOGISTIC REGRESSION ANALYSIS WITH BLEEDING EPISODES AS AN INDEPENDENT VARIABLE

The patient identified as the outlier in Figures 8 and 13 had a very low predicted probability (0.005) of developing thrombocytopenia based on the ICU/CCU model, yet she did develop thrombocytopenia after a bleeding episode. This case suggested that bleeding might be a risk indicator for the development of thrombocytopenia. As well, other risk indicators identified in the baseline (gastrointestinal, GI bleed, and musculoskeletal/connective tissue admission diagnosis) and ICU/CCU (FFP and PRBC transfusions, and gastrointestinal and musculoskeletal/connective tissue most responsible diagnosis,) models suggested that bleeding episodes might have been related to the development of thrombocytopenia. Recently, Stephen *et al* (1999) identified episodes of bleeding as an independent risk factor for thrombocytopenia in a prospective study in surgical ICU patients (Table 1). For these reasons, in order to explore the contribution of bleeding to the development of thrombocytopenia, all bleeding episodes, including GI bleeds, upon admission to the unit were grouped together. Similarly, all patients who experienced any bleeding episodes in the ICU/CCU, including GI bleeds, were grouped together to generate data for the new variable.

Since bleeding episodes was not identified *a priori* as a risk indicator, criteria used to document a bleeding episode had not been prepared. Thus, for this exploratory analysis, information on patients who suffered a bleeding episode was obtained from notes made by the physician or nurse in the patient's medical chart or from verbal communication with the physician or nurse.

Figure 13 **Scatter plot of Studentized Residuals and Predicted Probability for the ICU/CCU Model**

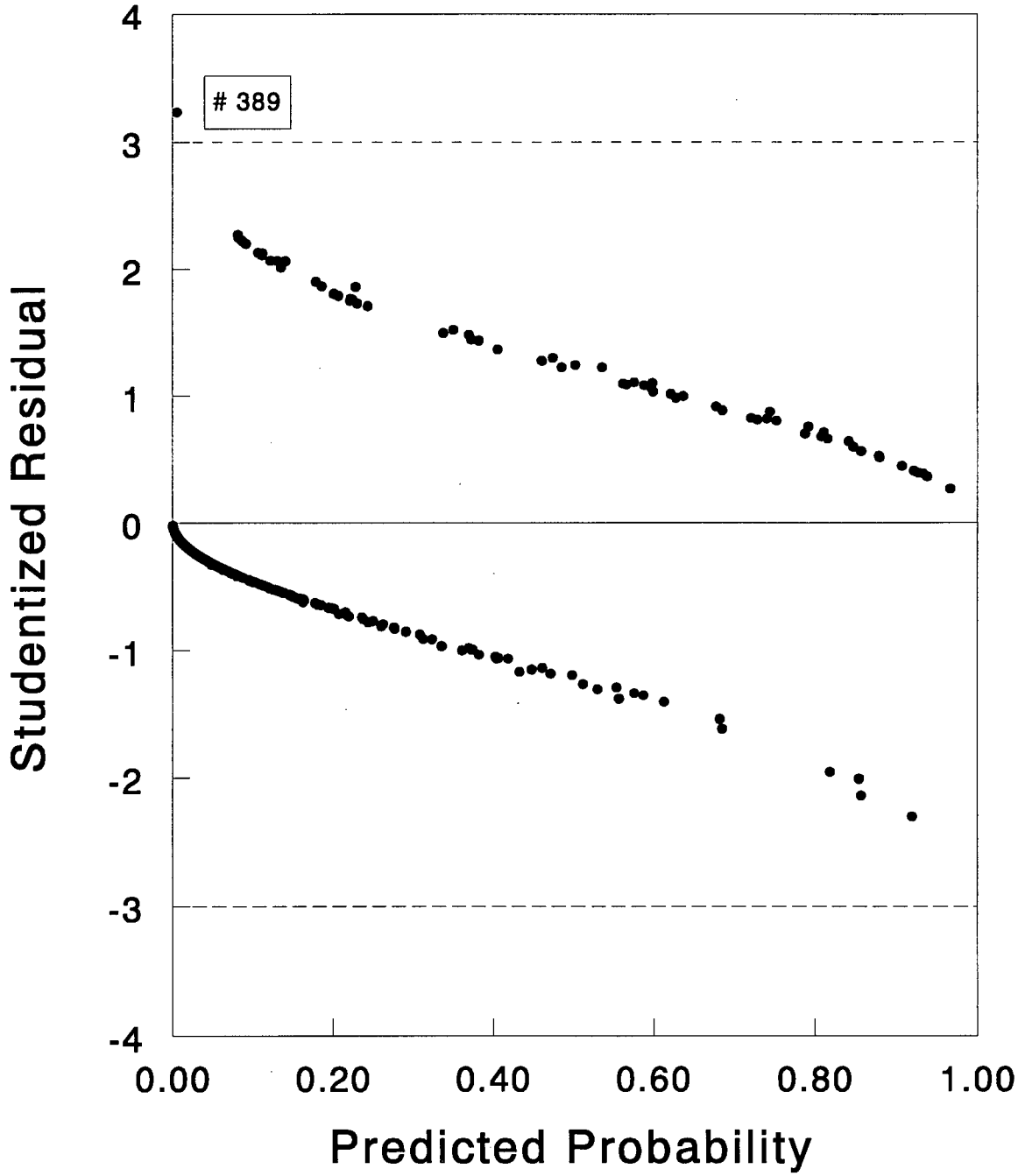


Figure 14 **Scatter plot of Leverage and Predicted Probability for the ICU/CCU Model**

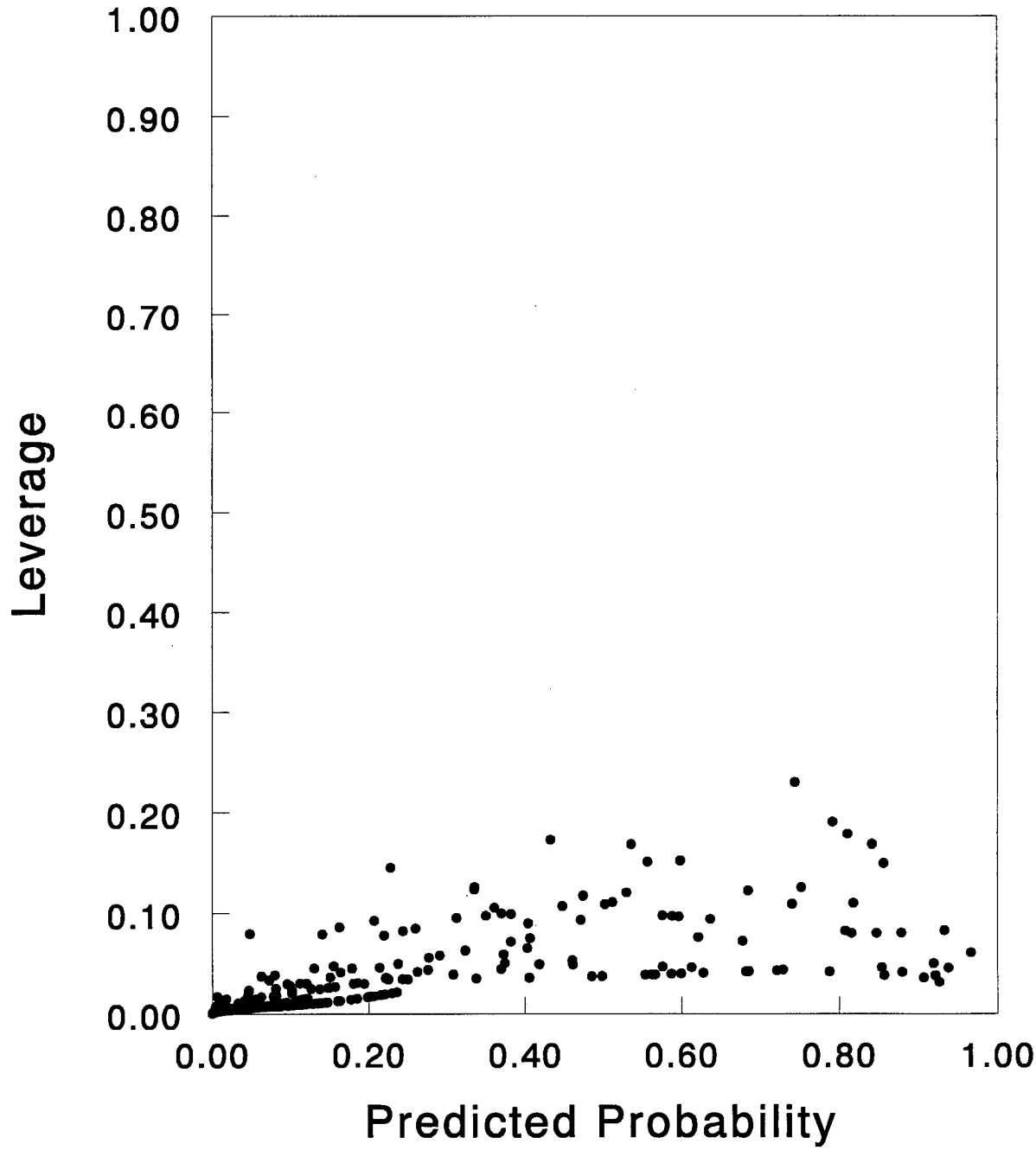


Figure 15 **Scatter plot of Cook's Distance and Predicted Probability for the ICU/CCU Model**

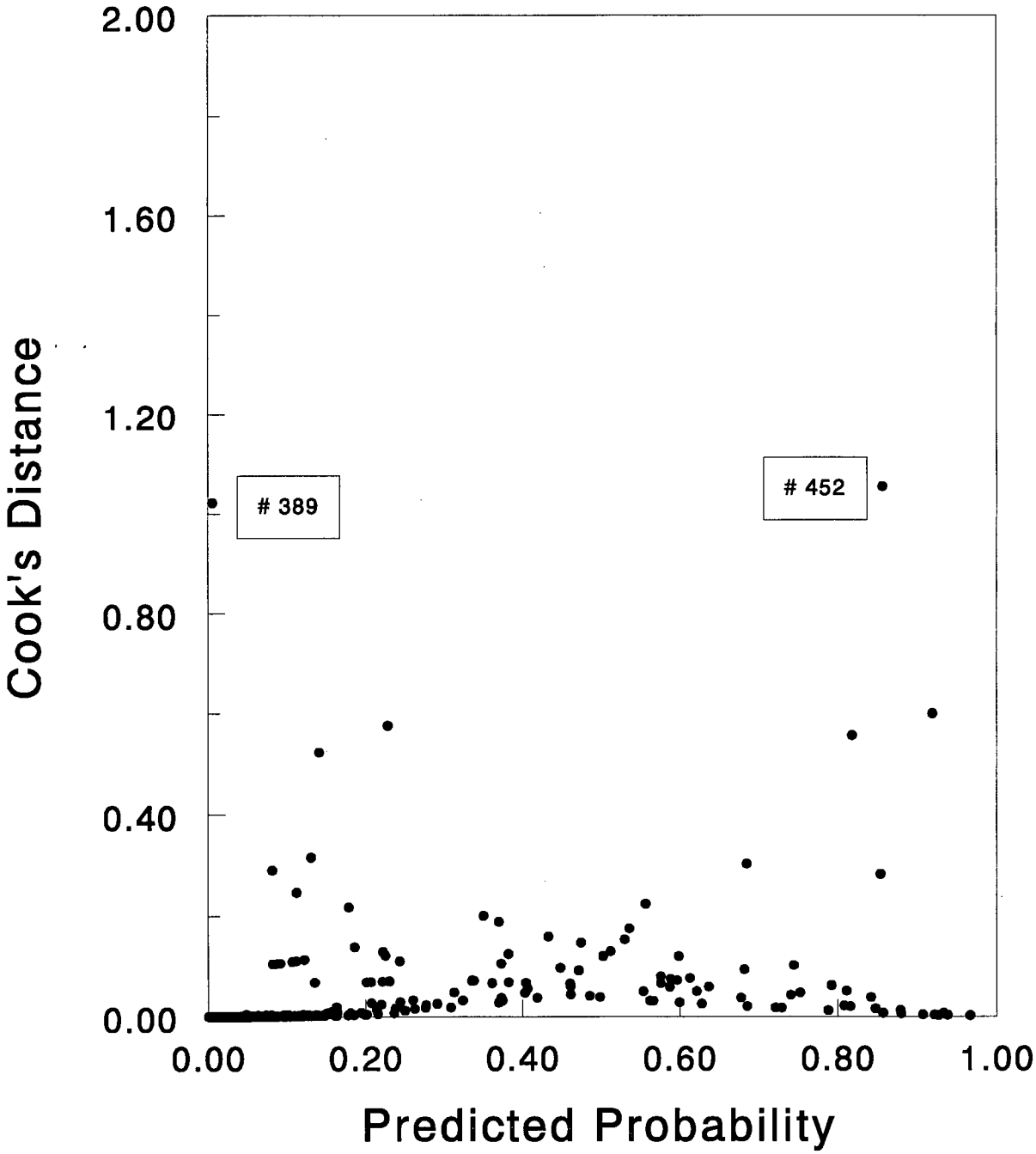
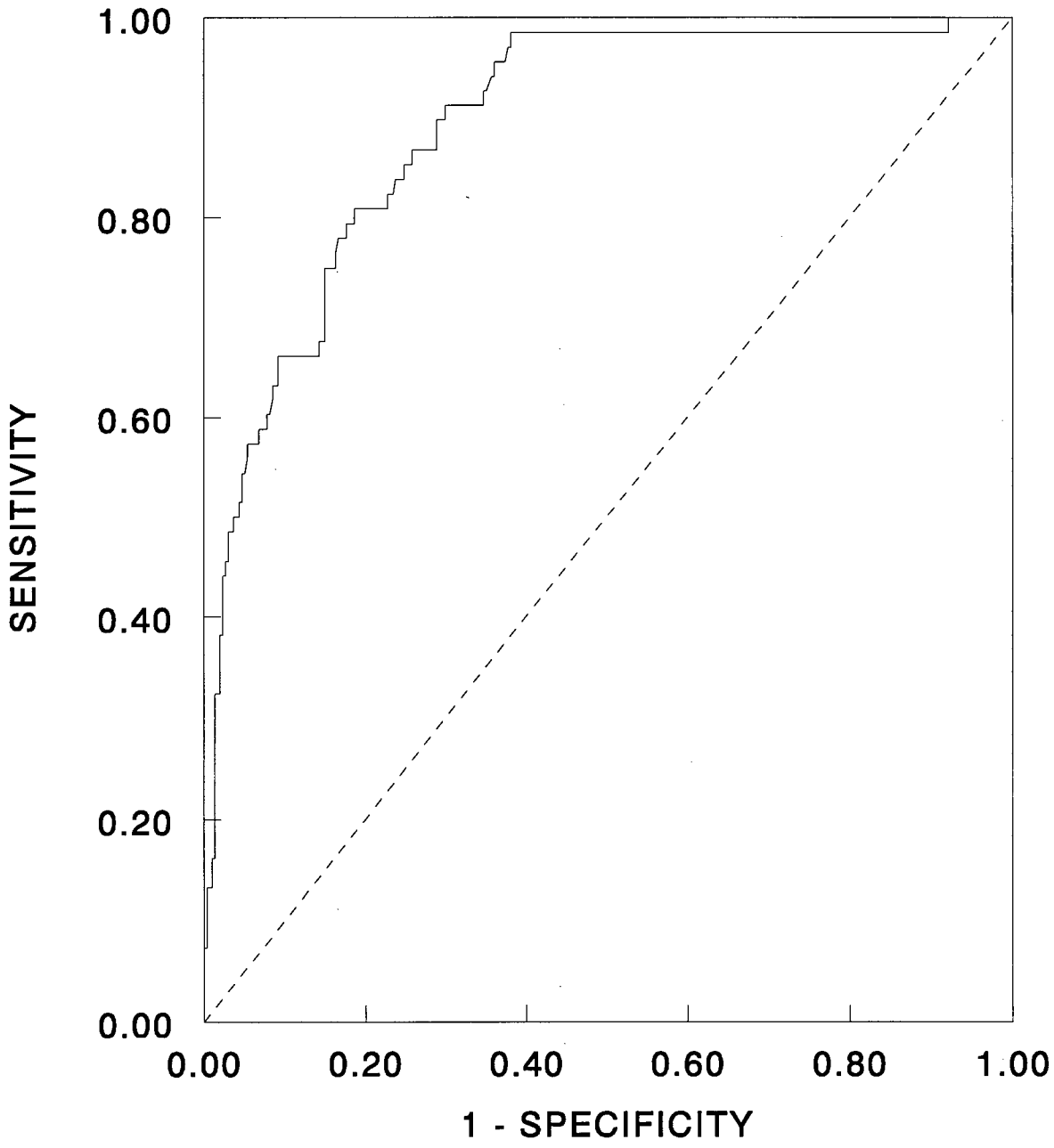


Figure 16 **Receiver operating characteristic curve for the ICU/CCU model**

The dotted line represents a c index of 0.5, which indicates the model has no discrimination ability. [c index = 0.891]



3.4.1 Exploratory logistic regression analysis of baseline variables

This analysis included 12 of the 13 baseline risk indicators (excluding GI bleed) and the new variable bleeding episodes, which included GI bleeds and hemorrhage upon admission to the unit. Bleeding episodes was associated with the development of thrombocytopenia following univariate analysis (Chi-square $p < 0.001$). These 13 variables were assessed for collinearity and were not found to have a high degree of association with each other.

Table 20 shows the multivariate model generated from these 13 variables. This model was very similar to the baseline model shown in Section 3.2.1.2, the only difference being the replacement of GI bleeds in the initial baseline model with bleeding episodes in the exploratory model. The model parameters (Table 20) and statistics (Table 21) were very similar to those of the initial baseline model (Table 10 and 11). The inclusion of a new variable for bleeding episodes did not convey any additional information or enhance the model.

Interactions among the 8 variables in the exploratory baseline model were investigated, and 3 of these met the criterion of $p \leq 0.05$. However, when each interaction was entered into the model, none appeared to enhance the fit and hence, no interaction term was added to the exploratory baseline model.

Regression diagnostic analyses were performed to evaluate the exploratory baseline model. As in the initial baseline model (Section 3.2.1.4), patient # 389 had a studentized residual greater than 3 SD and was identified as an outlier in the scatter plot of Cook's distance and predicted probability. As indicated previously (Section 3.2.1.4), the data for this patient were checked for correct entry into the database.

The area under the ROC curve or c index for the exploratory baseline model was 0.849 (95% CI: 0.799 – 0 900), which was similar to that of the initial baseline model of 0.847 (95% CI: 0.796 – 0.898) and indicated good association between the predicted probability of developing thrombocytopenia and the actual observed development of thrombocytopenia.

TABLE 20

MULTIVARIATE EXPLORATORY BASELINE MODEL FOR THE DEVELOPMENT OF THROMBOCYTOPENIA

Variable	Coefficient (β)*	Standard Error**	Wald	Odds Ratio	95% CI OR	p-Value
Sepsis	2.68	0.81	11.03	14.53	2.99-70.46	0.0009
Gastrointestinal Diagnosis	2.05	0.66	9.66	7.78	2.13-28.38	0.0019
Bleeding Episodes	1.58	0.58	7.45	4.85	1.56-15.09	0.0063
Musculoskeletal/ Connective Tissue	1.49	0.70	4.45	4.42	1.11-17.58	0.0348
Respiratory Non-Surgery	0.79	0.41	3.75	2.20	0.99-4.90	0.0527
APACHE II score[a]	0.091	0.018	26.79	1.10	1.06-1.13	< 0.0001
Age[b]	-0.11	0.05	4.37	0.90	0.81-0.99	0.0367
Admission Platelet Count[c]	-0.74	0.16	21.44	0.47	0.35-0.65	< 0.0001
Constant	1.10	0.93	1.41			0.2347

* estimated slope of the regression line

** standard error of the coefficient beta

[a] = per 1 unit increase. A change in the log odds β for an increase of 1 unit in the APACHE II score.

[b] = per 5 year increase. A change in the log odds β for an increase of 5 years of age.

[c] = per 50×10^9/L increase. A change in the log odds β for an increase of 50×10^9/L in the admission platelet count.

Regression Equation for the Baseline Model:

logit (thrombocytopenia) = 1.10 + 2.68 (sepsis) + 2.05 (gastrointestinal) + 1.58 (bleeding episode) + 1.49 (musculoskeletal/connective tissue) + 0.79 (respiratory non-surgery) + 0.09 (APACHE II score) - 0.74 (admission platelet count) – 0.11 (Age)

TABLE 21

EXPLORATORY BASELINE MODEL LOGISTIC REGRESSION STATISTICS

Model Statistics	Initial Baseline Model	Exploratory Model
-2 Log-Likelihood	258.93	257.72
Cox-Snell R^2	0.22	0.22
Nagelkerke R^2	0.36	0.36
Observed vs. Predicted Pearson's R^2	0.28	0.28
Hosmer-Lemeshow Goodness-of-fit	$p = 0.52$	$p = 0.39$
Overall Correct Classification	84.3%	84.8%
Sensitivity	39.7%	39.7%
Specificity	94.6%	95.2%

3.4.2 Exploratory logistic regression analysis of ICU/CCU variables

This analysis included 24 of the 25 risk indicators (excluding GI bleed) identified by univariate analyses of the ICU/CCU risk indicators and a new variable accounting for all bleeding episodes that occurred at admission and those that occurred during a patient's ICU/CCU stay up to the development of thrombocytopenia or discharge/death if he/she did not develop thrombocytopenia. Thirty-four patients had a bleeding episode in the ICU/CCU and this new variable was associated with thrombocytopenia following univariate analysis (Chi-square $p < 0.001$). In addition, these 25 variables were assessed for collinearity and were not found to have a high degree of association with each other.

Table 22 shows the multivariate model generated from these 25 variables. This model is similar to the ICU/CCU model shown in Table 15 with the following differences: 1) the exploratory model included 10 independent risk indicators, whereas the initial ICU/CCU model had 9 independent risk indicators; 2) PRBC transfusion was no longer a risk indicator, but bleeding episodes appeared as an independent risk indicator in the exploratory model; and 3) medication class inotropes appears as an independent risk indicator in the exploratory ICU/CCU model. All other risk indicators independently associated with the development of thrombocytopenia in the initial ICU/CCU model appeared in the exploratory ICU/CCU model. The model parameters (Table 22) and statistics (Table 23) were very similar to those of the initial ICU/CCU model (Table 15 and 16). There was a small increase in sensitivity in exploratory ICU/CCU (54.4% vs. 51.5%), which suggests that the new variable for bleeding episodes conveyed slightly more information about the study patients.

Interactions among the 10 variables in the exploratory ICU/CCU model were investigated (Table 24). There were 6 interactions that were statistically significant. Two of these interactions (admission platelet count by musculoskeletal/connective tissue most responsible diagnosis and class inotropes by ASA) were entered into the model; however, neither appeared to enhance the model and hence, were not added to the exploratory ICU/CCU model. The other 4 interactions (admission platelet count by sepsis, admission platelet count by class inotropes, admission platelet count by bleeding episodes, and class inotropes by swan-ganz catheter insertion) were also not added as they did not result in a major enhancement of the exploratory model.

Regression diagnostic analyses were performed to evaluate the exploratory ICU/CCU model. As in the initial ICU/CCU model (Section 3.2.2.5), patient # 389 had a studentized residual greater than 3 SD and was identified as an outlier in the scatter plot of Cook's distance and predicted probability. The data for this patient were checked for correct entry into the database.

The area under the ROC curve or c index for the exploratory ICU/CCU model was 0.898 (95% CI: 0.859 – 0 937), which was similar to that of the initial ICU/CCU model of 0.891 (95% CI: 0.851 – 0.932) and indicates good association between the predicted probability of developing thrombocytopenia and the actual observed development of thrombocytopenia.

3.5 CLINICAL OUTCOMES

3.5.1 Thrombocytopenia and hemorrhage

A total of 26 patients (7.2%) experienced a hemorrhage at some time during their ICU/CCU stay (Table 25). However, only 2 (2.9%) of the 68 thrombocytopenic patients developed a hemorrhagic event after the occurrence of thrombocytopenia. Thirteen (19.1%) of the 68 thrombocytopenic patients had a hemorrhagic event at the time of or a few days before the onset of thrombocytopenia. In addition, of the 294 patients who did not develop thrombocytopenia, 11 (3.7%) experienced a hemorrhage at some point during their stay on the unit.

3.5.2 Thrombocytopenia and length of ICU/CCU and hospital stay

The mean lengths of ICU/CCU and hospital stay among the 68 thrombocytopenic patients and the 294 non-thrombocytopenic patients are presented in Table 25. Patients who developed thrombocytopenia had longer ICU/CCU and hospital stays than those who did not develop thrombocytopenia. In addition, the mean length of ICU/CCU and hospital stay among the ICU and CCU patients, based on admission

TABLE 22

MULTIVARIATE EXPLORATORY ICU/CCU MODEL FOR THE DEVELOPMENT OF THROMBOCYTOPENIA

Variable	Coefficient (β)*	Standard Error**	Wald	Odds Ratio	95% CI OR	p-Value
FFP Transfusion	3.14	1.17	7.20	23.13	2.33-229.56	0.0073
Sepsis	2.82	0.79	12.66	16.71	3.54-78.85	0.0004
Musculoskeletal/ Connective Tissue	2.21	0.69	10.37	9.10	2.37-34.89	0.0013
Swan Ganz	1.71	0.44	14.84	5.51	2.31-13.13	0.0001
Gastrointestinal	1.45	0.70	4.25	4.26	1.07-16.88	0.0393
Bleeding Episodes	1.18	0.51	5.32	3.24	1.19-8.79	0.0211
Respiratory Non-Surgery	0.83	0.46	3.24	2.30	0.93-5.70	0.0717
Class Inotropes	0.78	0.45	2.94	2.17	0.90-5.27	0.0001
ASA	-0.81	0.39	4.27	0.45	0.21-0.96	0.0388
Admission Platelet Count[a]	-0.88	0.19	21.46	0.41	0.29-0.60	< 0.0001
Constant	1.38	0.81	2.90			0.0886

* estimated slope of the regression line

** standard error of the coefficient beta

[a] = per 50×10^9/L increase. A change in the log odds β for an increase of 50×10^9/L in the admission platelet count.

Regression Equation for the ICU/CCU Model:

logit (thrombocytopenia) = 1.38 + 3.14 (FFP transfusion) + 2.82 (sepsis) + 2.21 (musculoskeletal/connective tissue) + 1.71 (swan ganz) + 1.45 (gastrointestinal) + 1.18 (bleeding episodes) + 0.83 (respiratory non-surgery) + 0.78 (class inotropes) - 0.81 (ASA) - 0.88 (admission platelet count)

TABLE 23

EXPLORATORY ICU/CCU MODEL LOGISTIC REGRESSION STATISTICS

Model Statistics	Initial Baseline Model	Exploratory Model
-2 Log-Likelihood	226.19	221.45
Cox-Snell R^2	0.29	0.30
Nagelkerke R^2	0.47	0.48
Observed vs. Predicted Pearson's R^2	0.37	0.38
Hosmer-Lemeshow Goodness-of-fit	$p = 0.15$	0.59
Overall Correct Classification	87.3%	87.6%
Sensitivity	51.5%	54.4%
Specificity	95.6%	95.2%

TABLE 24

INTERACTIONS AMONG VARIABLES IN THE EXPLORATORY ICU/CCU MODEL

Interaction	-2 Log-Likelihood	G	Df	p-value
Main Effects	221.447			
Admission platelet count * ASA	220.803	0.644	1	0.42
Admission platelet count * FFP Transfusion	220.980	0.467	1	0.49
Admission platelet count * Gastrointestinal	221.383	0.064	1	0.80
Admission platelet count * Musculoskeletal	**217.763**	**3.684**	**1**	**0.05**
Admission platelet count * Respiratory no surgery	221.437	0.010	1	0.92
Admission platelet count * Sepsis	**213.830**	**7.617**	**1**	**< 0.01**
Admission platelet count * Class Inotropes	**216.169**	**5.278**	**1**	**0.02**
Admission platelet count * Swan Ganz	218.482	2.965	1	0.09
Admission platelet count * bleeding episodes and GI Bleed	**215.829**	**5.618**	**1**	**0.02**
ASA * Gastrointestinal	220.495	0.952	1	0.33
ASA * Musculoskeletal	220.887	0.560	1	0.45
ASA * Respiratory no surgery	220.984	0.463	1	0.50
ASA * Sepsis	220.215	1.232	1	0.27
ASA * Class Inotropes	**217.870**	**3.577**	**1**	**0.06**
ASA * Swan Ganz	219.203	2.244	1	0.13
ASA * bleeding episodes and GI Bleed	221.416	0.031	1	0.86
FFP Transfusion * Gastrointestinal	221.402	0.045	1	0.83
FFP Transfusion * Respiratory no surgery	219.884	1.563	1	0.21
FFP Transfusion * Class Inotropes	220.625	0.822	1	0.36
FFP Transfusion * Swan Ganz	220.096	1.351	1	0.25
FFP Transfusions * Bleeding episodes & GI Bleeds	220.625	0.822	1	0.36
Gastrointestinal * Class Inotropes	219.533	1.914	1	0.17
Gastrointestinal * Swan Ganz	220.279	1.168	1	0.28
Gastrointestinal * Bleeding episodes & GI Bleeds	220.352	1.095	1	0.30
Musculoskeletal * Class Inotropes	220.554	1.393	1	0.24
Musculoskeletal * Swan Ganz	220.554	1.393	1	0.24
Musculoskeletal * Bleeding episodes & GI Bleeds	221.278	0.169	1	0.68
Respiratory no surgery * Class Inotropes	221.350	0.097	1	0.75
Respiratory no surgery * Swan Ganz	221.394	0.053	1	0.82
Respiratory no surgery * Bleeding episodes & GI Bleeds	221.302	0.145	1	0.70
Sepsis * Class Inotropes	218.723	2.724	1	0.10
Sepsis * Swan Ganz	221.447	0.000	1	0.99
Class Inotropes * Swan Ganz	**216.119**	**5.328**	**1**	**0.02**
Class Inotropes * Bleeding episodes & GI Bleeds	221.368	0.079	1	0.78
Swan Ganz * Bleeding episodes & GI Bleeds	220.863	0.584	1	0.45

and most responsible diagnosis, are shown in Table 26. Patients with an ICU admission or most responsible diagnosis had longer lengths of ICU/CCU and hospital stay than CCU patients. The designation of admission or most responsible diagnosis did not have an effect on the length of ICU/CCU and hospital stay among ICU or CCU patients, respectively.

3.5.3 Thrombocytopenia and mortality

Twenty-five patients expired in the ICU/CCU during the one-year study period, and the mortality rate among patients who developed thrombocytopenia was markedly higher than that among patients who did not develop thrombocytopenia (Table 25). Following discharge from the ICU/CCU, 13 more patients expired on the ward at LGH, three of whom had developed thrombocytopenia while in the ICU/CCU. Mortality data for patients transferred to other hospitals could not be obtained. Furthermore, mortality among ICU and CCU patients based on admission and most responsible diagnosis is shown in Table 27. Patients with an ICU admission or most responsible diagnosis had a higher mortality rate than did patients with a CCU admission or most responsible diagnosis. The designation of admission or most responsible diagnosis did not have an effect on the mortality among ICU or CCU patients, respectively.

3.5.4 Number of medications administered

The mean number of medications (± SD) that were administered to patients up to the day they developed thrombocytopenia was 12.9 ± 5.2. The mean number of medications (± SD) administered to patients who did not develop thrombocytopenia (up to discharge or death) was 13.0 ± 6.1.

3.5.5 Discontinuation of heparin therapy

Clinicians often discontinue heparin therapy in ICU/CCU patients who develop thrombocytopenia due to a concern regarding HIT and the resultant risk of life- or limb-threatening thrombosis. Of the 57 study patients who developed thrombocytopenia and received heparin, 10 (17.5%) had their heparin discontinued within 24 hours of the onset of thrombocytopenia.

TABLE 25

CLINICAL OUTCOMES AMONG THE PATIENTS ADMITTED TO THE ICU/CCU

Clinical Outcome	Thrombocytopenia (N = 68)	No Thrombocytopenia (N = 294)	p-value*
Hemorrhage	2 (2.9%)	11 (3.7%)	0.003
Length of ICU/CCU Stay			< 0.001
Mean ± SD	12.3 ± 13.5	4.5 ± 4.8	
Range	1 – 57	1 – 37	
Length of Hospital Stay			< 0.001
Mean ± SD	32.0 ± 39.0	14.5 ± 18.3	
Range	3 – 216	1 – 175	
Mortality	12 (17.6%)	13 (4.4%)	< 0.001

* Independent t-test for continuous variables and chi-square analysis for dichotomous variables

TABLE 26

LENGTH OF ICU/CCU AND HOSPITAL STAY BASED ON ADMISSION AND MOST RESPONSIBLE DIAGNOSIS

Clinical Outcome	ICU Admission Diagnosis (N = 173)	ICU Most Responsible Diagnosis (N = 172)	CCU Admission Diagnosis (N = 189)	CCU Most Responsible Diagnosis (N = 190)
Length of ICU/CCU Stay				
Mean ± SD	8.2 ± 10.5	8.1 ± 10.6	4.0 ± 3.4	4.1 ± 3.2
Range	1 – 57	1 – 57	1 – 21	1 – 21
Length of Hospital Stay				
Mean ± SD	24.8 ± 31.3	24.6 ± 31.3	11.4 ± 13.0	11.6 ± 13.3
Range	1 – 216	1 – 216	1 – 117	1 – 117

TABLE 27

MORTALITY AMONG THE ICU/CCU STUDY PATIENTS

BASED ON ADMISSION AND MOST RESPONSIBLE DIAGNOSIS

Clinical Outcome	ICU Admission Diagnosis (N = 173)	ICU Most Responsible Diagnosis (N = 172)	CCU Admission Diagnosis (N = 189)	CCU Most Responsible Diagnosis (N = 190)
Mortality				
In ICU/CCU	15 (8.7%)	15 (8.7%)	10 (5.3%)	10 (5.3%)
On Ward	7 (4.0%)	7 (4.1%)	6 (3.2%)	6 (3.2%)
Total	22 (12.7%)	22 (12.8%)	16 (8.5%)	16 (8.5%)

DISCUSSION

4.1 DEMOGRAPHIC CHARACTERISTICS AND DEVELOPMENT OF THROMBOCYTOPENIA

Of the 935 patients admitted to the ICU/CCU, 573 were excluded from the study, primarily for having less than two platelet counts performed or having an admission platelet count $< 150 \times 10^9$/L. The 362 patients who comprised the study sample (Table 3) were mainly male (63%) with a mean age of 63 years. Caucasians comprised 88% of the study sample.

The critical care unit at LGH admits both ICU and CCU patients; however, the unit does not distinguish between an ICU and a CCU diagnosis on admission. Based on *a priori* criteria, the most common ICU admission diagnoses were respiratory non-surgery, infection, gastrointestinal, and musculoskeletal/connective tissue. Among CCU patients, the most frequent admission diagnoses were acute myocardial infarction, unstable angina, and cardiovascular non-surgery (Table 4). There were slightly more CCU (52%) than ICU (48%) patients admitted to the unit (Table 5).

The most responsible diagnosis was obtained from the discharge summary, which explicitly requires the physician to designate the diagnosis most responsible for ICU/CCU stay. Among ICU patients, the diagnoses most frequently designated as most responsible were respiratory non-surgery, infection, and gastrointestinal; whereas among CCU patients, acute myocardial infarction, cardiovascular non-surgery, and unstable angina were most frequently recorded. In the majority of cases, the most responsible diagnoses were the same as the admitting diagnoses (Table 4). However, a change in a patient's status during the ICU/CCU stay resulted in most responsible diagnosis different than the admitting diagnosis in 48 (13.3%) cases. In most of these cases, patients with unstable angina (chest pain) on admission were found to have acute myocardial infarction or CHF during the ICU/CCU stay. As well, 7 patients admitted to the unit had most responsible diagnoses that differed from their admission diagnoses because of development of sepsis (4 cases) or seizures (3 cases) while on the unit.

The mean acute physiology (APS) and APACHE II scores for the study sample were 11.3 (95% CI: 10.4 – 12.2) and 15.4 (95% CI: 14.5 – 16.4), respectively. The acuity of illness among patients with

an ICU admission diagnosis was higher than patients with a CCU admission diagnosis based on the APACHE II scores, 19 (95% CI: 17.3 – 20.4) and 12 (95% CI: 11.3 – 13.4) respectively. With this range of APACHE II scores, ICU patients would be considered to be mildly to moderately critically ill (Knaus *et al.*, 1985). The distributions of the APS and APACHE II scores were noted to be fairly wide and positively skewed. The level of skewness was greater among ICU than CCU patients (Figures 3 and 4), which likely reflects the wider range of admission diagnoses.

It is difficult to compare the basic demographic characteristics of patients in the present study with those in the five other studies that have investigated thrombocytopenia in critically ill patients because of the different populations investigated. These other studies included patients in a medical ICU at a university hospital (Baughman *et al.*, 1993), a combined medical-surgical ICU at a tertiary care community hospital (Bonfiglio *et al.*, 1993), a trauma ICU at a university hospital (Hanes *et al.*, 1993), a surgical-trauma ICU (Cawley *et al.*, 1993), and a surgical ICU at a teaching hospital (Stephan *et al.*, 1999). The first four of these studies were conducted in the United States, whereas the fifth study by Stephan *et al* (1999) was conducted in France. Thus, the present study differed markedly from previous ones as it involved a community-based hospital that admits ICU and CCU patients to the same unit. In order to obtain a reasonable comparison, the subset of patients with an ICU diagnosis on admission will be considered.

Only two of the previous studies documented admission diagnoses. Baughman *et al* (1993) reported that gastrointestinal bleeding, drug overdose, respiratory failure, and severe infection were the most common diagnoses leading to admission in their study sample; whereas in the study by Bonfiglio *et al* (1995), cardiovascular (not defined), pulmonary, neurologic, and gastrointestinal were the most common primary admission diagnostic classifications. The admissions related to gastrointestinal and respiratory disorders, as well as infection, indicate some similarity with the present study. It is difficult to make a more specific comparison due to the lack of detail provided by the authors. It is interesting to note that in the studies by Baughman *et al* (1993) and Bonfiglio *et al* (1995), cardiovascular diagnoses on admission were identified in 7% and 20% of patients, respectively, though details were not provided.

The APACHE II is a severity of disease classification instrument (Knaus *et al.*, 1985). Of the 5 studies mentioned above, only one reported APACHE II scores (Stephan *et al.*, 1999). From their data, it can be calculated that the mean APACHE II score was 17.5 and the 95% CI of the mean was 15.1 – 19.9. This is similar to the mean APACHE II Score of 19 (95% CI: 17.3 – 20.4) observed among ICU patients in the present study. While the APACHE II score is an important indicator of severity of disease that may be related to thrombocytopenia and other outcomes in ICU patients, the lack of information from previous studies precludes a comprehensive comparison.

4.2 ADMISSION PLATELET COUNTS AND INCIDENCE OF THROMBOCYTOPENIA

The mean (± SD) admission platelet count of patients enrolled in the study was 246×10^9/L ± 79 $\times 10^9$/L, which was within the normal range for platelet count determination at LGH ($150 – 400 \times 10^9$/L). Based on admission diagnoses, the mean (± SD) admission platelet counts of ICU patients was 254×10^9/L ± 87×10^9/L and that of CCU patients was 239×10^9/L ± 69×10^9/L.

In a retrospective study involving 314 mixed medical-surgical ICU patients by Bonfiglio *et al* (1995), the investigators observed a mean (± SD) admission platelet count of 264×10^9/L ± 115×10^9/L. Using data from a group of 63 trauma ICU patients (Hanes *et al.*, 1997), the calculated mean (± SD) admission platelet count was calculated to be 233×10^9/L ± 73×10^9/L. Patients in both of these studies had admission platelet counts in the normal range as was observed in ICU patients in the present study. The authors of the three other studies investigating thrombocytopenia in critically ill patients (Baughman *et al.*, 1993; Cawley *et al.*, 1999; Stephan *et al.*, 1999) did not report admission platelet counts and it is unclear whether they included admission platelet count in their regression analyses.

Overall, the observed incidence of thrombocytopenia, defined as two consecutive platelet counts $< 150 \times 10^9$/L, was 18.8% (95% CI: 14.8% - 22.8%). However, the study sample was comprised of ICU and CCU patients and the incidence of thrombocytopenia was markedly different in these two subgroups: 29.7 % (95% CI: 22.9% - 36.5%) among ICU patients and 8.9% (95% CI: 4.9% - 12.9%) among CCU patients.

As this is the first prospective study to investigate thrombocytopenia among consecutive CCU patients of all diagnoses, the observed incidence is a novel finding. The relatively low incidence of thrombocytopenia reflects the fact that CCU patients are mainly comprised of acute myocardial infarction and unstable angina patients who are not generally considered critically ill. While no previous study has directly assessed the overall incidence of thrombocytopenia in CCU patients, authors have performed secondary analyses of data from previous clinical trials of specific drug therapies in groups of cardiovascular patients to investigate the occurrence and incidence of thrombocytopenia (McClure *et al.*, 1999; Harrington *et al.*, 1994). For example, McClure *et al* (1999) reported an overall incidence of thrombocytopenia of 7% (based on their data, the 95% CI for thrombocytopenia was calculated to be 6.5% - 7.5%) in 9217 acute coronary syndrome patients enrolled in "the platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) study" in which patients had been randomized to eptifibatide- and placebo-treated arms. These authors defined thrombocytopenia as a nadir platelet count $< 100 \times 10^9$/L, or a decrease of > 50% from baseline. Only 0.5% of CCU patients in the present study (Table 7) had one platelet count $< 100 \times 10^9$/L, while the number of patients with > 50% decline in their platelet count from baseline was not recorded. In addition, it is important to note that parenteral platelet glycoprotein IIb/IIIa receptor inhibitor use has been associated with thrombocytopenia (platelet count $< 100 \times 10^9$/L), with an incidence of approximately 5% (Tcheng, 2000; Stringer, 1999; Madan and Berkowitz, 1999). However, it is possible that some of the cases of thrombocytopenia observed were caused by a concomitant medication. For example, patients who received platelet glycoprotein IIb/IIIa inhibitors typically received heparin therapy, which may be associated with the development of thrombocytopenia (Tcheng, 2000; Madan and Berkowitz, 1999). Platelet glycoprotein IIb/IIIa inhibitors were not administered to any patients at LGH and were not available at the hospital during the data collection period.

The incidence of thrombocytopenia among ICU patients in the present study was similar to the reported incidences of 23% to 35% in medical, surgical, or mixed medical-surgical ICU patients (Baughman *et al.*, 1993; Bonfiglio *et al.*, 1995; Stephan *et al.*, 1999), and 13% and 41% in mixed surgical-trauma (Cawley *et al.*, 1999) and trauma patients (Hanes *et al.*, 1997), respectively. While these

other studies reported different definitions for thrombocytopenia, it was possible to obtain data from each of them based on the definition of one platelet count $< 100 \times 10^9$/L. Of the 172 ICU patients in the present study, 27 (15.7%; 95% CI: 10.2% - 21.0%) exhibited one platelet count less than 100×10^9/L (Table 7). This is at the lower end of the range of incidences observed in the five studies referred to above.

In the present study, the approach taken to define thrombocytopenia was more rigorous than that of the previous studies by requiring 2 consecutive platelet counts below the threshold. There is considerable inter-and intra-day variability in the platelet count, and these were observed to be 11% and 1% - 7% (mean 2.9%), respectively, in the present study. Given this variability, it is possible that in previous studies patients had a transient, isolated decline in platelet count below the threshold employed. In the present study, for example, 27 of 172 (15.7%) ICU patients would have met the criterion of one or more platelet counts $< 100 \times 10^9$/L for thrombocytopenia; whereas in 5 of those patients, the decline in platelet count below 100×10^9/L was an isolated event (Table 7).

Two previous studies defined severe thrombocytopenia as one or more platelet counts $< 50 \times 10^9$/L. In a retrospective study involving 162 medical ICU patients, Baughman *et al* (1993) observed an incidence of 10%; while in a prospective study by Hanes *et al* (1997), the authors observed an incidence of 3.2% using this criterion. These reported incidences of severe thrombocytopenia are similar to the 7% of ICU patients that would have been classified as severely thrombocytopenic in the present study. It has been suggested that platelet counts below 50×10^9/L represent a marked increased risk for spontaneous bleeding (Warkentin and Kelton, 2000; Wazny and Ariano, 2000), though studies in different populations have not been done (Wazny and Ariano, 2000; Levine, 1999; Arrowsmith *et al.*, 1999). It is also interesting to note that, using this criterion for thrombocytopenia, only 0.5% of CCU patients in the present study would have been classified as having experienced severe thrombocytopenia. The higher incidence of severe thrombocytopenia occurring in patients with ICU admissions may reflect a greater disease severity in these patients.

In the present study, a platelet count threshold for thrombocytopenia of 150×10^9/L was utilized. This represents the lower bound of the normal range at LGH ($150 - 400 \times 10^9$/L) and is analogous to

clinicians using the lower bound of normal to identify other abnormal clinical laboratory indices. Previous studies have used 100×10^9/L as the threshold for thrombocytopenia, perhaps because the risks for bleeding are considered to increase when the platelet count declines below this level (Williams *et al.*, 1995; Bithell, 1993). However, little prospective work has been done in different patient populations (Wazny and Ariano, 2000) and it is not clear what degree of thrombocytopenia may significantly affect hemostasis, especially in a critical care setting (Harrington *et al.*, 1994).

Patients in the ICU setting are often treated with heparin (Wazny and Ariano, 2000; Bonfiglio *et al.*, 1995), which may increase their risk for bleeding at any particular platelet count (Warkentin and Kelton, 2000; Hirsh *et al.*, 1998). In addition, heparin can cause an immune-mediated thrombocytopenia, referred to as heparin-induced thrombocytopenia (HIT), which, paradoxically, increases the risk of life-threatening thrombosis. In an often-cited paper, Warkentin *et al* (1995) defined thrombocytopenia in patients at risk for HIT as a decrease in the platelet count to below 150×10^9/L, 5 or more days after starting heparin therapy. Thus, in the present study, the threshold of 150×10^9/L was selected because it marks the lower bound of the normal range and is consistent with a commonly used definition.

4.3 LOGISTIC REGRESSION MODELLING

Regression analysis investigates the ability of one or more independent variables to predict a patient's status with regard to a dependent variable (Guyatt *et al.*, 1995). More simply stated, regression explores the strength of the relationship between one or more independent variables and a specific dependent variable. This statistical technique is useful in constructing predictive models that may be of use in clinical decision making. Logistic regression is a technique being used in clinical research (Concato *et al.*, 1993), and a number of authors have commented that this technique provides a logical and consistent approach to developing predictive models when working with dichotomous dependent variables (Hosmer and Lemeshow, 1991; Concato *et al.*, 1993; Vollmer, 1996). However, there are no uniform statistical criteria that define the best model from a set of data, and thus, many issues must be

considered including the risk indicators identified, goodness of fit, collinearity, interactions, and regression diagnostics to determine whether the model is reasonable.

4.3.1 Baseline and ICU/CCU models

In the present study, two different models were constructed. The first was a baseline model to identify risk indicators for thrombocytopenia present at the time patients were admitted to the ICU/CCU. The second was an ICU/CCU model, which was formulated using risk indicators present upon admission to the unit plus those that patients were exposed to while in the unit. The reason for constructing these two different models was to identify underlying or baseline risk indicators for thrombocytopenia and determine whether subsequent events or interventions would alter patients' risk for developing thrombocytopenia. The analysis of baseline risk for the development of thrombocytopenia is unique to the present study, as earlier researchers did not address this issue.

An important objective when generating a predictive model is to minimize the number of variables so that the final model is more likely to be numerically stable, and can be easily generalized to similar patient populations (Hosmer and Lemeshow, 1989a). For the present study, previous literature was examined to identify risk indicators suspected to be associated with the development of thrombocytopenia in critically ill patients. There were 126 potential risk indicators identified *a priori*, 24 of which were baseline variables and the remainder were related to intervention or events experienced by patients during the ICU/CCU stay. Following descriptive and univariate analyses, the number of candidate variables was further reduced, leaving an enriched set of variables to be included in multivariate logistic regression analysis. However, there is always the possibility that some variables were excluded by chance, or by lack of patient exposure to that intervention or event.

4.3.1.1 Baseline model

Of the 24 potential baseline variables identified *a priori*, 13 were selected as candidate variables following descriptive and univariate analyses. Multivariate logistic regression analysis identified 8 baseline risk indicators as being independently associated with the development of thrombocytopenia.

These included five admission diagnoses (sepsis, gastrointestinal, GI bleed, musculoskeletal/connective tissue, and respiratory non-surgery), as well as age, APACHE II score, and the admission platelet count (Table 10). Six of the 8 baseline risk indicators were associated with an increased risk for the development of thrombocytopenia. Only increased age and higher admission platelet count were associated with a decreased risk for the development of thrombocytopenia. A diagnosis of sepsis was associated with the largest odds ratio for the development of thrombocytopenia (OR 14.1; 95% CI: 2.9 – 67.9). Based on the baseline model, the predicted probability of developing thrombocytopenia for a patient admitted to the unit with the mean admission platelet count, APACHE II score, and age, and none of the other predictive risk indicators, would be 0.08 (Figure 7). Patients admitted with a higher admission platelet count or age would have a reduced predicted probability of developing thrombocytopenia, whereas patients exhibiting a higher than average APACHE II score or any one of the dichotomous risk indicators would have an increased predicted probability. For example, if a patient had an average platelet count and diagnosis of sepsis on admission, the predicted probability of developing thrombocytopenia would be increased to 0.55. Patients exposed to more risk indicators would have a higher predicted probability for developing thrombocytopenia. For example, using the equation shown in Table 10, the predicted probability of developing thrombocytopenia for a 60 year old patient admitted with a platelet count of 200×10^9/L, an APACHE II score of 30, and sepsis on admission would be 0.92.

The baseline model was a reasonable fit of the observed data. The overall correct classification was 84.3%, which means the model correctly predicted 84% of the outcomes (i.e. thrombocytopenia or no thrombocytopenia) among the 362 patients in the study sample. This classification is based on a decision threshold of 0.50, which means that if a patient's predicted probability was ≥ 0.50, he/she would be predicted to develop thrombocytopenia. The sensitivity of the model was 40%, indicating that the model correctly identified 27 of the 68 patients who were observed to have developed thrombocytopenia, and this low sensitivity indicates a relatively high false negative rate. The specificity of the model was 95%, demonstrating that the model had good ability in correctly predicting patients who were observed not to have developed thrombocytopenia.

A receiver operating characteristic (ROC) curve describes the discriminative ability of a model for predictive purposes (Metz, 1978). The receiver of the predictive information can operate at any point on the curve using a particular decision threshold. When used to assess a predictive model such as the present baseline model for thrombocytopenia, the area under the (ROC) or c index is the estimated probability that for a randomly chosen pair of patients, the patient developing thrombocytopenia is the one having the higher predicted probability (i.e. the predicted and observed outcomes are concordant) (Harrell *et al.*, 1985). A c index of 1 perfectly ranks patients according to the severity of their outcomes (e.g. thrombocytopenia), whereas a c index of 0.5 indicates that the model has no discrimination ability. The area under the ROC curve or c index of the final baseline model was 0.85, which demonstrates that it had good performance, was a reasonable fit of the observed data, and was good at discriminating between patients who did and who did not develop thrombocytopenia.

Goodness of fit tests are used in assessing how well models classify or describe the observed data (Hosmer and Lemeshow, 1991). A model is considered to be a reasonable fit of the observed data if a high p-value is obtained with the Hosmer-Lemeshow Goodness of Fit test (see Section 2.2.2.2.7). Of the various models examined, the present baseline model had the highest p-value. Based on the experience obtained developing models in this investigation, it became clear that the Hosmer-Lemeshow Goodness of Fit test statistic and corresponding p-value are very sensitive to relatively small changes in the model. This has been observed by others (John Spinelli, personal communication, 1999).

The likelihood is the probability of the observed results, given the parameter estimates (Hosmer and Lemeshow, 1989). A good model is one that results in a high likelihood of the observed results, which yields a small value for –2 log-likelihood. For a model that fits perfectly, the likelihood is one, and –2 times the log-likelihood is 0. The present baseline model had the lowest –2 log-likelihood when compared to other models with different candidate variables.

The Pearson correlation (r) was also calculated and then squared to describe the degree of association between observed and predicted outcomes. It is a number between –1 and 1 and is used to measure the association between the model predicted probabilities and the observed occurrence of thrombocytopenia (Mittlbock and Schemper, 1996). A value of $r^2 \geq 0.30$ suggests a model with a good fit

(John Spinelli, personal communication, 1999). The r^2 value for the baseline model was 0.28 and supported the selection of this model as a reasonable fit of the observed data.

Risk indicators identified as independently associated with the development of thrombocytopenia were tested for interactions, to ensure that the effect of one risk indicator for the development of thrombocytopenia was not dependent on the value of another risk indicator. Although there were three statistically significant interactions among the eight baseline risk indicators (Table 12), these did not enhance the fit of the model and thus, were not included.

Regression diagnostics were performed to examine the adequacy of the resulting model. This is important for identifying cases that the model does not fit well, cases that exert a strong influence on the coefficient estimates, and variables that are highly related to each other (Concato *et al.*, 1993; Hosmer and Lemeshow, 1991). In general, publications involving studies utilizing logistic regression analysis have been characterized by deficiencies in the performance or reporting of regression diagnostics (Concato *et al.*, 1993). By not performing regression diagnostics, errors such as overfitting and collinearity can occur. As well, outliers can result in the generation of a spurious model, especially from studies with small sample sizes (Concato *et al.*, 1993; Hosmer and Lemeshow, 1991).

Regression diagnostics performed on the baseline model identified one patient as a potential outlier. However, after checking for correct data entry and ensuring that this patient met the indications for admission, this patient's data were included in the analysis. She was a 62 year-old female admitted to the ICU/CCU with unstable angina, a relatively low APACHE II score of 9, and an admission platelet count of 464×10^9/L. By her third day in the unit her platelet count had decreased to 141×10^9/L, coincident with a hemorrhagic event. Her platelet count continued to decline and on the fourth day had reached a nadir of 115×10^9/L, at which time she met the study criteria for thrombocytopenia. She was discharged from the unit on the fifth day with a platelet count of 127×10^9/L. This patient did not receive any blood transfusions; however, ASA was being administered, and a Swan-Ganz catheter was inserted when she became hemodynamically unstable on day 2. Intravenous heparin was discontinued on the day of the hemorrhage, however, small amounts of heparin (6 units/hr) were continually infused through the Swan-Ganz catheter to maintain patency. Thus, this patient had a high admission platelet count, a CCU

admission diagnosis, and was receiving ASA, which suggested a low predicted probability of developing thrombocytopenia according to the baseline model (predicted probability 0.002), and therefore, she was identified as a possible outlier. When her data were removed from the data set and logistic regression rerun, the resulting model and goodness of fit were not affected qualitatively or quantitatively and thus, this patient was included in the final analysis. While no details are available, it is possible that the thrombocytopenia experienced by this patient was associated with the hemorrhagic event during her ICU/CCU stay.

Consideration of risk indicators identified by a multivariate logistic regression model can give some information about the underlying factors responsible for the outcome (e.g. thrombocytopenia). In the present study, age was associated with a decreased risk for developing thrombocytopenia, as indicated by an odds ratio less than one. In the study by Hanes *et al* (1997), age was associated with an increased risk for development of thrombocytopenia in critically ill trauma patients. However, their study involved ICU patients and their model included variables present on admission and those encountered during ICU stay. In the present study, approximately half the patients admitted were relatively young ICU patients and the other half tended to be older cardiac patients with a markedly lower risk for development of thrombocytopenia (Table 6). Therefore, age was investigated as a surrogate marker for a cardiac related admission diagnosis by substituting a single variable for the 3 cardiac diagnoses and redoing multivariate logistic regression analysis. When this was done, CCU admission diagnosis did not replace age as a risk indicator in the model, suggesting that age was not simply a surrogate marker for CCU admission diagnosis, and was providing additional information. Furthermore, it suggests there were other factors involved in the apparent protective effect of age in the patient study sample.

Increased admission platelet count was associated with a decreased risk for the development of thrombocytopenia. Patients who had an admission platelet count close to the threshold of 150×10^9/L were more likely to develop thrombocytopenia, because a relatively small decline would have been sufficient to have dropped their platelet counts below the threshold. Stephan *et al* (1999) also reported that higher admission platelet count was associated with a decreased risk for thrombocytopenia. In another study (Bonfiglio *et al.*, 1995), the baseline (admission) platelet count accounted for the largest

proportion of the variance for the development of thrombocytopenia following stepwise linear regression analysis.

APACHE II score, an indicator of severity of illness, was also an independent risk indicator identified by the baseline model as being associated with the development of thrombocytopenia. Stephan *et al* (1999) reported that an APACHE II score > 15 was associated with the development of thrombocytopenia in surgical ICU patients. Other researchers have also reported that severely ill patients with sepsis and respiratory failure (Baughman *et al.*, 1993; Bonfiglio *et al.*, 1995; Cawley *et al.*, 1999) were more likely to develop thrombocytopenia. However, these authors did not use any specific diagnostic scale, such as the APACHE II score, to assess disease severity upon admission to the ICU. Hanes *et al* (1997) used the trauma score (Champion *et al.*, 1981) to assess severity of the injury. However, it is difficult to compare the APACHE II score and the trauma score as measures of disease severity as different parameters are used in their calculation.

Gastrointestinal (GI) bleeding was another risk indicator independently associated with the development of thrombocytopenia in the baseline model: 4 of the 10 (40%) patients with an admission diagnosis of a GI bleed developed thrombocytopenia. It is possible that a GI bleed was associated with thrombocytopenia due to blood loss and platelet consumption. Circulating platelets are utilized in the normal hemostatic system to limit blood loss (Handin, 1994a). Patients with a platelet count between 50 – 100 $\times$ 10^9/L have an increased propensity to bleed and the incidence of bleeding increases as the platelet count decreases below 50 $\times$ 10^9/L (Williams, 1995; Coller and Schneiderman, 2000). Because of the inclusion criteria, no patients in this study had an admission platelet count less than 150 $\times$ 10^9/L; the lowest admission platelet count for the 10 patients with an admission diagnosis of GI bleed was 157 $\times$ 10^9/L (range 157 - 606 $\times$ 10^9/L). Thus, a low platelet count was likely not the reason for the GI bleed. There have been many reports of thrombocytopenia preceding GI bleeds (Levine, 1999; Arrowsmith *et al.*, 1999), but no study has specifically demonstrated that GI bleeds are associated with the development of thrombocytopenia. However, bleeding episodes have been reported to result in patients becoming thrombocytopenic (Warkentin and Kelton, 2000; Davis, 1998; Handin, 1994; Lind, 1995). There have been no studies reporting GI bleeds as a risk indicator for the development of thrombocytopenia,

however, Stephan *et al* (1999) found that, in surgical ICU patients, episodes of bleeding were independently associated with the development of thrombocytopenia.

Sepsis has been reported to be associated with platelet injury, resulting in systemic removal of platelets (Bogdonoff *et al.*, 1990). Thrombocytopenia likely occurs in septic patients due to decreased platelet survival, probably a result of increased peripheral destruction in the microvasculature (Gawaz *et al.*, 1995; Bogdonoff *et al.*, 1990), disseminated intravascular coagulation (DIC) (Bogdonoff *et al.*, 1990; Neame *et al.*, 1980; Kelton *et al.*, 1979), or toxic bone marrow suppression (Bessman and Gardner, 1983; Bogdonoff *et al.*, 1990). Platelet activation and degranulation have been reported to occur in septic patients (Gawaz *et al.*, 1995; Hinshaw *et al.*, 1982). Thrombocytopenia has been reported to occur early in the course of sepsis and has been attributed to enhanced platelet destruction (Neame *et al.*, 1980; Bogdonoff *et al.*, 1990). Increased formation of platelet aggregates and enhanced platelet clearance occur in septic patients, indicating activated platelets do not remain in the circulation, but rather are cleared (Gawaz *et al.*, 1995). In the present study, patients admitted with sepsis had a higher APACHE II score and thus, were more severely ill; the mean APACHE II score for septic patients was 21, whereas it was 15 for non-septic patients. An association between sepsis and thrombocytopenia has been reported in previous studies involving critically ill patients (Baughman *et al.*, 1993; Bonfiglio *et al.*, 1995; Cawley *et al.*, 1999; Stephan *et al.*, 1999; Bogdonoff *et al.*, 1990; Lee *et al.*, 1993; Brun-Buisson *et al.*, 1995; Oppenheimer *et al.*, 1976; Wilson *et al.*, 1982; Milligan *et al.*, 1974).

DIC is associated with the development of thrombocytopenia (Bogdonoff *et al.*, 1990; Bonfiglio *et al.*, 1995; Neame *et al.*, 1980; Kelton *et al.*, 1979). However, none of the patients in the present study were noted to have developed DIC. Tests to confirm the presence of this condition such as fibrinogen levels, fibrin split products, and D-dimer tests were ordered only once during the study period: this patient was not diagnosed with DIC.

Musculoskeletal/connective tissue diagnosis was also identified as a risk indicator in the baseline model. Most of the patients with an admission diagnosis of musculoskeletal/connective tissue had suffered a traumatic injury (71%), usually due to motor vehicle accidents, skiing accidents, or falls. Even though most of these patients were noted to have suffered blood loss, no correlation was observed

between musculoskeletal/connective tissue admission diagnosis and PRBC transfusion. It is possible that the loss of blood experienced by these patients resulted in the development of thrombocytopenia. Platelets are lost during the hemorrhage and consumed at the site of the injury, which could have resulted in a decrease in the platelet count. Hanes *et al* (1997) noted that non-head injury was independently associated with the development of thrombocytopenia in patients admitted to a trauma ICU and is the only study to have investigated the effect of trauma on the occurrence of thrombocytopenia.

Respiratory non-surgery was another baseline risk indicator for thrombocytopenia. Respiratory failure and ARDS have been reported by other researchers (Heffner *et al.*, 1987; Schneider RC *et al.*, 1980; Bone *et al.*, 1976) to be associated with the development of thrombocytopenia. Bone *et al* (1976) observed that 19 of 30 consecutive ARDS patients admitted to a medical ICU developed thrombocytopenia (defined as a platelet count $< 150 \times 10^9$/L). DIC was diagnosed in 7 of these patients, while the remaining 12 patients had no have evidence of DIC. Haynes *et al* (1980) conducted a study investigating coagulation and fibrinolysis involving 26 critically ill patients; 14 were diagnosed with ARDS, and 12 were at high risk, but did not develop the syndrome. The authors reported that platelet counts were not significantly different in the ARDS group compared to those in the non-ARDS group at 36 and 60 hours. However, in both groups there was a statistically significant ($p < 0.01$) decrease in platelet count over the 60-hour sampling period. In a study investigating platelet number and turnover in 15 patients with severe acute respiratory failure, Schneider *et al* (1980) reported that 10 patients developed platelet counts less than 100×10^9/L. They noted that platelet survival was reduced by almost two thirds in all 15 patients and platelet sequestration was demonstrated in the lungs, and the reticuloendothelial system (spleen and liver). Altered hemostasis has been reported to be commonly observed in patients with ARDS and acute respiratory failure (Bogdonoff *et al.*, 1990). However, the site and mechanism of platelet destruction and the pathophysiologic role of the platelet remain unclear. In a study investigating risk factors associated with the development of thrombocytopenia, Bonfiglio *et al* (1995) reported that respiratory failure, in combination with sepsis syndrome/septic shock, was associated with thrombocytopenia.

Gastrointestinal diagnosis was identified as a risk indicator in the baseline model. Gastrointestinal disorders, such as small bowel diverticula, inflammatory bowel disease, and ulcerative colitis, have been reported to be associated with thrombocytopenia (Klee *et al.*, 1997; Mones, 1983; Kocoshis *et al.*, 1979). In the present study, gastrointestinal diagnosis included both surgery and non-surgery patients. Surgery is an invasive procedure and can involve blood loss, both of which are associated with the development of thrombocytopenia (Bogdonoff *et al.*, 1990). Surgical procedures had been performed in 9 of 14 patients with gastrointestinal admission diagnosis, in all cases within 24 hours prior to admission to the unit. No study performed in critically ill patients reported gastrointestinal diagnosis being associated with thrombocytopenia. Bonfiglio *et al* (1995) investigated gastrointestinal admission diagnosis as a potential variable for the development of thrombocytopenia. They did not report it to be associated with thrombocytopenia following univariate analysis, even though a greater proportion of their patients (11.1%) had this diagnosis on admission compared to 3.9% in the present study.

The present study is unique in that it is the first study to generate a baseline model and provide useful information on risk indicators present on admission. However, the low sensitivity suggests that other factors present at admission or encountered during the ICU/CCU stay are important contributors to the development of thrombocytopenia.

It is important to note that the models developed by the authors of previous studies were based on variables present on admission and those occurring in the ICU. In addition, these studies involved different patient populations from the present study.

4.3.1.2 ICU/CCU model

Of the 126 potential risk indicators identified *a priori*, 25 were selected as candidate variables following descriptive and univariate analyses. Candidate variables selected included the individual medications ASA, imipenem, and salbutamol. In order to account for the low frequency of exposure to individual medications, classes of medications that were chemically and pharmacologically similar were defined. Three classes of medications were selected as candidate variables following descriptive and univariate analyses: inotropes, cephalosporins, and H_2-antagonists. Daily heparin dose was also

associated with the development of thrombocytopenia following descriptive and univariate analyses, however, it had a negative beta coefficient, and therefore appeared protective for thrombocytopenia. This is in contrast to results of studies in animals (Copley and Robb, 1941; Copley and Robb, 1942a) and humans (Gollub and Ulin, 1962; Davey and Lander, 1968; Saffle *et al.*, 1980; Schwartz *et al.*, 1985) that have demonstrated a dose dependent decrease in platelet count associated with heparin.

Multivariate logistic regression analysis identified nine risk indicators as being independently associated with the development of thrombocytopenia. These included four most responsible diagnoses (sepsis, musculoskeletal and connective tissue, gastrointestinal diagnosis, and respiratory non-surgery), three interventions/procedures (FFP and PRBC transfusion, and Swan-Ganz catheter insertion), one medication (ASA) and admission platelet count (Table 15). Only ASA and higher admission platelet count were associated with a decreased risk for the development of thrombocytopenia. Transfusion of FFP was associated with the largest odds ratio for the development of thrombocytopenia (OR 20.0; 95% CI: 2.0 – 199.2). The risk indicator with the next highest odds ratio for developing thrombocytopenia was sepsis (OR 15.1; 95% CI: 3.1 – 74.3). Based on the ICU/CCU model, the predicted probability of developing thrombocytopenia for a patient admitted to the unit with the mean admission platelet count ($246 \pm 79 \times 10^9$/L) would be 0.06 (Figure 12). Patients admitted with a higher admission platelet count or those receiving ASA therapy would have a reduced predicted probability of developing thrombocytopenia, whereas patients exposed to any of the dichotomous risk indicators would have an increased predicted probability. For example, if a patient had an average platelet count and received a transfusion of FFP, the predicted probability of developing thrombocytopenia would be increased to 0.56. Patients exposed to more risk indicators would have a higher predicted probability for developing thrombocytopenia. For example, using the equation illustrated in Table 15, the predicted probability of developing thrombocytopenia for a patient with sepsis, a Swan-Ganz catheter and an admission platelet count of 200×10^9/L would be 0.94.

There were three risk indicators identified by the baseline model that were no longer present in the ICU/CCU model: age, APACHE II score, and a diagnosis of GI bleed. In addition, there were four new risk indicators identified in the ICU/CCU model: FFP and PRBC transfusions, Swan-Ganz catheter

insertion, and ASA. Three of these new risk indicators tend to occur more in ICU than CCU patients. For example, Swan-Ganz catheter insertion, PRCB, and FFP transfusions occurred in 64.1%, 78.9%, and 88.9% of ICU patients as compared to 35.9%, 21.1%, and 11.1% of CCU patients, respectively. On the other hand, only 15.5% of ICU patients received ASA as compared to 84.5% of CCU patients.

The ICU/CCU model was a reasonable fit of the observed data and provides an improvement in predicting the development of thrombocytopenia over the baseline model. The overall correct classification improved from 84% with the baseline model to 87% with the ICU/CCU model. The specificity improved very slightly from 95% to 96%, demonstrating that the ICU/CCU model continued to exhibit good ability in correctly predicting patients who were observed not to have developed thrombocytopenia. The largest improvement was seen in the sensitivity of the ICU/CCU model. This model correctly identified 52% of patients observed to have developed thrombocytopenia compared to 40% by the baseline model. This suggests that data collected during ICU/CCU stay provided additional information relative to baseline data in predicting which patients developed thrombocytopenia.

The area under the ROC curve (c index) of the ICU/CCU model was 0.89, indicating this model was a reasonable fit of the observed data, and was good at discriminating between patients who did and who did not develop thrombocytopenia. This was a small improvement relative to the baseline model (0.89 vs. 0.85).

The final ICU/CCU model is considered to be a reasonable fit in terms of describing the observed data as demonstrated by a high p-value ($p = 0.15$) obtained with the Hosmer-Lemeshow Goodness of Fit test. In addition, the present ICU/CCU model had the lowest –2 log-likelihood when compared to other models with different combinations of candidate variables. The Pearson r^2 of 0.37 also supported this model as a reasonable fit of the observed data.

Regression diagnostics performed on the ICU/CCU model identified one patient as being a potential outlier, the same patient identified by the baseline model. As discussed earlier (Section 4.3.2), her data were entered correctly and this patient met the indications for admission to the ICU/CCU as a cardiac patient. Excluding this patient's data from the analysis did not affect the model qualitatively or quantitatively, and thus, her data were included in the analysis. She was a potential outlier because she

developed thrombocytopenia, despite a very low model predicted probability (0.005) of developing thrombocytopenia.

It has been noted (Concato *et al.*, 1993) that model fitting, regression diagnostics, and tests for interactions are often omitted, not reported, or not done when multivariate methods, including logistic regression are performed, which leads to questionable models. It is important to note that none of the other studies investigating thrombocytopenia in critically ill patients reported model fitting, regression diagnostics, or tests for interactions.

Indicators identified in the ICU/CCU model can provide some information about the underlying factors responsible for thrombocytopenia. There were 5 risk indicators identified in the present ICU/CCU model that were also identified in the baseline model: admission platelet count; and four most responsible diagnoses including of sepsis, gastrointestinal, musculoskeletal/connective tissue, and respiratory non-surgery. The possible role of these 5 risk indicators have already been discussed (Section 4.3.2). The 4 other risk indicators, Swan-Ganz catheter, FFP transfusion, PRBC transfusion, and ASA are discussed below.

Swan-Ganz (pulmonary artery) catheter insertion was associated with the development of thrombocytopenia. Other researchers have noted Swan-Ganz catheters to have a local or systemic anti-platelet effect, as implicated by their association with the development of thrombocytopenia (Bonfiglio *et al.*, 1995; Bogdonoff *et al.*, 1990; Kim *et al.*, 1980; Miller *et al.*, 1984; Layon, 1999; McNulty *et al.*, 1998; Rull *et al.*, 1984). Interestingly, in three of these studies (Kim *et al.*, 1980; Miller *et al.*, 1984; Rull *et al.*, 1984), the platelet count never dropped below the threshold for thrombocytopenia used in the present study (i.e. 150×10^9/L), but there was a "statistically significant" drop in the platelet count from baseline. In addition, in a prospective study involving 193 critically ill mixed surgical-trauma patients, Cawley *et al* (1999) observed that insertion of invasive central or arterial lines was independently associated with thrombocytopenia. In a retrospective study of 162 medical ICU patients, Baughman *et al* (1993) found that pulmonary artery catheter use was associated with thrombocytopenia following univariate analysis, but not after multivariate linear regression analysis. There is no proven explanation for the decline in the platelet count experienced by some patients following insertion of these catheters;

however, it is possible that the presence of a foreign surface can lead to non-immune platelet destruction (Bogdonoff *et al.*, 1990). Furthermore, heparin is bonded to the surface of Swan-Ganz catheters and low doses of heparin are continuously infused to keep them patent. However, as discussed in Section 4.3.3.1, heparin was not an independent risk indicator for thrombocytopenia in this study. Interestingly, patients who had a Swan-Ganz catheter inserted had a higher mean APACHE II score (27 ± 9) than patients without a Swan-Ganz catheter (13 ± 7), indicating that patients with a Swan-Ganz catheter inserted were more severely ill. Therefore Swan-Ganz catheters may have a direct effect on platelet count, but their use might also be a marker for greater disease severity, which was an independent indicator of thrombocytopenia in the baseline model.

The benefit of Swan-Ganz catheter use in critically ill patients has been debated for the past two decades (Connors *et al.*, 1996; Brandstetter *et al.*, 1998; Bender, 1999; Dalen and Bone, 1996; Robin, 1985). Several observational studies (Connors *et al.*, 1996; Bender, 1999) have reported increased mortality, hospital stay, and cost associated with the use of Swan-Ganz catheters in critically ill patients. There is no evidence from randomized controlled trials that insertion of Swan-Ganz catheters reduces morbidity or mortality. In addition, there are no data from clinical trials that provide indications for their use. There are several possible reasons why the use of these catheters has been associated with adverse outcomes (Connors *et al.*, 1996). First, Swan-Ganz catheters may directly result in poorer patient outcomes, presumably because the risks (deleterious effects) of these catheters outweigh their benefits. Second, use of Swan-Ganz catheters may indicate an invasive and aggressive style of care, leading to higher mortality rate and higher costs. And third, in response to the information provided by this catheter, the resulting change in therapy may lead to higher mortality. From the results of the present and one other study (Bonfiglio *et al.*, 1995) assessing risk indicators for the development of thrombocytopenia, Swan-Ganz catheters have been identified as being independently associated with the development of this condition. However, it is unclear whether Swan-Ganz catheters are causally related or a marker for some other process in the development of thrombocytopenia.

FFP transfusion was another risk indicator independently associated with the development of thrombocytopenia. Previous authors have noted FFP transfusions to be associated with a reduction in

platelet count (Brunner-Bolliger *et al.*, 1997; Noe *et al.*, 1982); however, no other study analyzing risk factors in critically ill patients identified FFP transfusion as an independent risk factor. FFP transfusions are used in patients who have multiple acquired coagulation factor deficiency (Bucur *et al.*, 2000). This includes patients with severe liver disease who may have low concentrations of vitamin K-dependent clotting factors (i.e. II, VII, IX X); patients who receive massive transfusions of PRBC, which lack coagulation factors; patients with DIC, usually due to a specific underlying cause; and patients who need a rapid reversal of the anticoagulant effect of warfarin because of active bleeding, emergency surgery, or serious trauma. Other indications for FFP transfusion include: severe factor V deficiency, exchange for thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome, congenital coagulation defects, and as an exchange transfusion in neonates. The thrombocytopenia associated with FFP transfusion in the current study could have been caused by the dilutional effect of PRBC administered with FFP (Bogdonoff *et al.*, 1990). Five patients who developed thrombocytopenia received both PRBC and FFP transfusions. Another explanation for the development of thrombocytopenia in patients administrated FFP transfusions has been postulated by several researchers (Nugent, 1992; Brunner-Bolliger *et al.*, 1997; Nijjar *et al.*, 1987; Scott *et al.*, 1988). Alloantibodies, present in transfused FFP, directed against the PI^{A1} antigen located on platelet glycoprotein (GP) IIIa receptor results in increased platelet destruction by macrophages in the reticuloendothelial system. In the present study, 9 patients were administrated FFP transfusions, of whom 6 developed thrombocytopenia. The quantity of FFP transfused among the 9 patients ranged from 2 to 8 units.

Another risk indicator identified in this study to be associated with the development of thrombocytopenia was PRBC transfusions. In previous studies, PRBC transfusions (Baughman *et al.*, 1993) and the number of PRBC transfusions administered (Hanes *et al.*, 1997) were associated with thrombocytopenia following univariate analyses. In the study by Cawley *et al* (1999), the authors did not analyze blood products as a variable in their linear regression model, but they noted that a limitation of their study was the lack of monitoring of blood products received. PRBC transfusions are generally indicated in anemic patients with clear evidence of impaired oxygen delivery, in the perioperative period where acute blood losses are > 25%, and in patients who have suffered trauma with an acute loss of blood

(Kruskall, 2000; Beutler and Masouredis, 1995). In all these cases, PRBC transfusions are needed to restore the oxygen-carrying capacity of blood. It has been reported (Bucur *et al.*, 2000; Bogdonoff *et al.*, 1990; Reed *et al.*, 1986; Noe *et al.*, 1982; Counts *et al.*, 1979; Murphy and Gardner, 1969) that large transfusions of blood will result in dilution of the platelet count. Riska *et al* (1988) noted that more than 20 units of whole blood transfused within 24 hours is a potential risk indicator for thrombocytopenia. The post-transfusional decline in platelet count can be ascribed to dilution of platelets in the circulation by blood products containing low concentrations of viable platelets (Bogdonoff *et al.*, 1990) or sequestration of platelets by the spleen following blood transfusions (Bareford *et al.*, 1987). The drop in the platelet count observed in patients transfused with PRBC has been observed to be related to the number of transfused units (Hanes *et al.*, 1997; Bogdonoff *et al.*, 1990; Counts *et al.*, 1979), and occurs relatively early after the transfusion. In the present study, the median number of units of PRBC transfused was only 2 (mean 3; range 1 – 12).

Two risk indicators, admission platelet count and ASA, were protective, or associated with a decreased risk of thrombocytopenia. Admission platelet count was discussed in section 4.3.2. No other study in critically ill patients has noted a protective effect of ASA on the development of thrombocytopenia. In the present study, CCU patients had a lower incidence of thrombocytopenia and these patients were routinely administered ASA for suspected acute myocardial infarction or unstable angina. A considerably higher percentage of the cardiac patients (85%) received ASA therapy than ICU patients (15%). Therefore, ASA was investigated as a surrogate marker for a cardiac diagnosis by substituting a single variable for the 3 cardiac diagnoses and redoing multivariate logistic regression analysis. When this was done, CCU admissions did not replace ASA, suggesting that ASA was not simply a surrogate marker for CCU most responsible diagnosis, but was providing additional information about patients' risk of developing thrombocytopenia. ASA is widely recognized as an irreversible platelet inhibitor (Ryan *et al.*, 1996), which could increase the risk of bleeding in some patients and potentially increase the risk of developing thrombocytopenia. Conversely, platelet inhibitors such as ASA may reduce platelet consumption in patients at risk and thus, a reduced risk of thrombocytopenia could be postulated. However, there is no published evidence to support such an effect of ASA.

There were no cardiac risk indicators identified as being associated with the development of thrombocytopenia neither in the present study, nor in other studies of thrombocytopenia in critically ill patients. There have been no studies performed specifically to investigate risk indicators associated with thrombocytopenia in CCU patients; however, there have been clinical trials in cardiac patients with specific diagnoses that have evaluated thrombocytopenia as a clinical outcome (McClure *et al.*, 1999; Berkowitz *et al.*, 1998). In a recent double-blind study (McClure *et al.*, 1999), patients presenting with acute coronary syndrome were randomized to receive the platelet glycoprotein IIb/IIIa inhibitor eptifibatide or placebo, in addition to other standard therapies, including heparin and ASA. The investigators also examined the incidence of thrombocytopenia, defined as one platelet count $< 100 \times 10^9$/L or a decrease in the platelet count of > 50% from baseline, and risk indicators associated with the development of thrombocytopenia. Thrombocytopenia occurred in 7% of enrolled patients, with an estimated 95% CI of 6.5% to 7.5% based on sample size, and a median time to onset of 4 days in both treatment arms. Patients who developed thrombocytopenia were older, non-white, weighed less, and had more cardiac risk indicators. In addition, these patients experienced more bleeding episodes and were reported to be more than twice as likely to experience moderate or severe bleeding after adjusting for confounders. Following univariate and multivariate regression modelling, ischemic events (stroke, myocardial infarction, death) were significantly ($p < 0.001$) associated with thrombocytopenia. Neither heparin nor eptifibatide was found to independently increase the risk of developing thrombocytopenia. Berkowitz *et al* (1998) reported an incidence of thrombocytopenia (nadir platelet count $< 100 \times 10^9$/L) of 3.9% in a 2009 patient randomized trial of placebo, abciximab (a human-murine chimeric monoclonal antibody fragment that binds to platelet glycoprotein IIb/IIIa receptors) bolus, or abciximab bolus plus a 12 hour infusion during high-risk coronary revascularization. Following multivariate logistic modelling, a lower baseline platelet count, older age, and lower weight were important predictors of thrombocytopenia. None of the patients in the present study were exposed to platelet glycoprotein IIb/IIIa receptor inhibitors.

From the baseline and ICU/CCU models derived in the present study, it appears that severity of illness and episodes of bleeding were two important groups of risk indicators associated with the

development of thrombocytopenia. The APACHE II score was independently associated with thrombocytopenia in the baseline model, but not in the ICU/CCU model. The mean APACHE II score was higher for patients who developed thrombocytopenia (21 ± 12) than it was for patients who did not develop thrombocytopenia (14 ± 8). It is possible that in the ICU/CCU model, risk indicators other than APACHE II score may be markers for severity of illness, including FFP transfusion, sepsis diagnosis, musculoskeletal/connective tissue (trauma) diagnosis, Swan-Ganz catheter, gastrointestinal diagnosis, PRBC transfusion, or respiratory non-surgery diagnosis.

Episodes of bleeding were not included in the regression analysis as an *a priori* candidate variable. Hemorrhage can be a manifestation of thrombocytopenia or can result in thrombocytopenia due to platelet loss and consumption (Coller and Schneiderman, 2000; Santoro and Eby, 2000). Severe thrombocytopenia leading to hemorrhage has previously been reported in reviews of case reports of drug-induced thrombocytopenia (George *et al.*, 1998; Rizvi *et al.*, 1999; Pedersen-Bjergaard *et al.*, 1998). Section 4.4 will explore bleeding episodes as a risk indicator in both the baseline and ICU/CCU models. In the present study, a number of risk indicators identified in both models appeared to be associated with bleeding: musculoskeletal/connective tissue (trauma) diagnosis, GI bleed diagnosis, gastrointestinal diagnosis, PRBC, and FFP transfusions. Thus, these may have been identified as independent risk indicators for the development of thrombocytopenia because they provided information about bleeding episodes.

Because indicators identified in the ICU/CCU model are comprised of variables present on admission and those encountered during the ICU stay, it was important to investigate interactions between these variables. There were 3 interactions that were associated with the development of thrombocytopenia; however, none of them appeared to enhance the model qualitatively or quantitatively.

4.3.1.2.1 Heparin forced into the ICU/CCU model

There is evidence that heparin is associated with non-immune and immune-related thrombocytopenia (Greinacher, 1995; Warkentin *et al.*, 1998; Warkentin and Barkin, 1999). In this study, increased heparin dose entered as a continuous variable (dose/day) was identified as a protective risk

indicator for thrombocytopenia by univariate analysis, but was not found to be independently associated with the development of thrombocytopenia following multivariate logistic regression analysis. Moreover, when heparin was forced into the final model as a dichotomous (overall use or use at low, medium, or high doses), or continuous variable, it did not improve the ICU/CCU model qualitatively or quantitatively. Therefore, information on heparin use did not appear to contribute any additional information regarding the development of thrombocytopenia.

High dose heparin therapy (> 16,000 units/day) was identified as protective for the development of thrombocytopenia following univariate analysis, but not following multivariate analysis. Heparin was widely used in the ICU/CCU, but was administered differently among ICU and CCU patients. ICU patients were generally administered moderate-dose heparin (5,000 units twice daily) subcutaneously in order to prevent venous thromboembolism, while CCU patients were generally administered high dose heparin (> 16,000 units daily) for acute myocardial infarction or unstable angina. It is possible that in the present study, high dose heparin was acting as a marker for CCU diagnosis, which was associated with a low incidence of thrombocytopenia.

It has been reported that administration of intravenous heparin to healthy volunteers results in a reduction in the platelet count (Gollub and Ulin, 1962; Davey and Lander, 1968; Saffle *et al.*, 1980; Schwartz *et al.*, 1985). These researchers suggested that heparin has a proaggregatory effect on circulating platelets, thus causing a transient decline in the platelet count, which normalizes upon the discontinuation of heparin therapy. This effect could partly explain the phenomenon referred to as non-immune heparin-associated thrombocytopenia (HAT) (Greinacher, 1995; Warkentin *et al.*, 1998).

Although Baughman *et al* (1993) and Bonfiglio *et al* (1995) noted an association between heparin and thrombocytopenia following univariate analysis in their study patients, neither group demonstrated an association between heparin and thrombocytopenia following multivariate regression analysis. In several other studies (Hanes *et al.*, 1997; Cawley *et al.*, 1999; Stephan *et al.*, 1999), which differed somewhat in methodology, no association between heparin and thrombocytopenia was observed in critically ill patients. In the present study, all sources of heparin administration were recorded. This included all subcutaneous and intravenous doses, and all flushes to keep lines patent, including continuous low dose

heparin administration in Swan-Ganz catheters and arterial lines. Heparin was infused into these two types of lines at a rate of 6 units per hour and nurses pumped an additional 100 units throughout the day to keep the lines patent. Despite careful documentation of heparin administration, heparin did not emerge as an independent risk indicator for the development of thrombocytopenia.

Heparin is also known to cause an immune response resulting in thrombocytopenia which is referred to as heparin-induced thrombocytopenia (HIT) (Greinacher, 1995; Warkentin *et al.*, 1998). HIT tends to occur 5 days or more after the initiation of heparin (Greinacher, 1995; Warkentin *et al.*, 1998) and does not appear to be dose related (Warkentin and Barkin, 1999). This effect of heparin is a clinical concern because it is associated with a paradoxical increase in life- or limb-threatening thrombosis (Greinacher, 1995; Warkentin *et al.*, 1998; Warkentin and Barkin, 1999). The incidence of HIT has been reported to be 1% to 3% (Greinacher, 1995; Warkentin *et al.*, 1995; Warkentin *et al.*, 1998) in various patient populations, but the incidence in critically ill patients has not been investigated. It is possible that some of the patients in the present study actually developed HIT, but that the incidence was too low for heparin to be identified as a risk indicator in the multivariate logistic regression ICU/CCU model.

In recent years, clinicians have begun to use low-molecular-weight-heparin (LMWH) to reduce the risk of thrombosis in ICU and CCU patients (Green *et al.*, 1994; Clagett *et al.*, 1995). The only LMWH available at the time of the study at Lions Gate Hospital was tinzaparin. As with heparin, tinzaparin were identified by univariate analysis to be associated with a reduced risk for the development of thrombocytopenia. However, as only one physician prescribed tinzaparin in a small number of patients (16), it was not included in multivariate logistic regression analysis. LMWHs have been reported to be associated with a lower incidence of HIT (Warkentin *et al.*, 1995; Warkentin *et al.*, 1998), and the one patient who received tinzaparin and developed thrombocytopenia had a variety of risk indicators, suggesting an increased risk of thrombocytopenia. This patient, a 19 year-old female, was admitted to the unit following trauma, including hemorrhage, from a motor vehicle accident. In addition, she received 2 units of packed red blood cells and underwent surgery for femoral nail insertion for a fractured femur prior to the development of thrombocytopenia. She also received cefazolin before and after surgery. Based on her risk indicators, her predicted probability for developing thrombocytopenia was 0.74.

4.4 EXPLORATION OF THE ROLE OF BLEEDING EPISODES IN THE DEVELOPMENT OF THROMBOCYTOPENIA

A number of the observed baseline and ICU/CCU risk indicators are associated with the propensity to bleed, and bleeding may contribute to the development of thrombocytopenia (Warkentin and Kelton, 2000; Davis, 1998; Handin, 1994; Lind, 1995). In a recent prospective study involving surgical ICU patients, Stephan *et al* (1999) identified episodes of bleeding to be an independent risk indicator for the development of thrombocytopenia, although they did not report specific criteria to define bleeding episodes. In another prospective study by Hanes *et al* (1997) involving critically ill trauma patients, the number of PRBC units transfused was associated with thrombocytopenia by univariate analysis. The investigators did not note the occurrence of bleeding episodes directly, but recorded the number of PRBC transfusions given to patients who had suffered loss of blood. They reported that 45 of 63 (71%) critically ill trauma patients were transfused with at least one unit of PRBCs. No other studies involving critically ill patients have investigated bleeding episodes as a risk indicator for thrombocytopenia. While clinicians are generally aware that bleeding causes platelet consumption, the secondary and tertiary literature does not specifically identify bleeding to be a risk indicator for the development of thrombocytopenia (Bogdonoff *et al.*, 1990; Warkentin and Kelton, 2000; Wazny and Ariano, 2000; George and El-Harake, 1995).

This issue was explored in the present ICU/CCU patient sample using logistic regression analyses. Since there was no *a priori* classification of bleeding episodes, a new variable, bleeding episodes, was created *post hoc*. The occurrence of bleeding episodes was noted by reviewing the patients' medical chart regarding bleeding or hemorrhage or from verbal communication with the patients' attending nurses or physicians. The variable replaced GI bleeds as a candidate variable for baseline and ICU/CCU logistic regression modelling.

4.4.1 Exploratory baseline model

Following multivariate logistic regression analysis, bleeding episodes was identified as a risk indicator in the baseline exploratory model. However, bleeding episodes did not provide additional

information or enhance the fit of the new model when compared to the initial baseline model. The overall correct classification, sensitivity, and specificity were very similar to the initial baseline model and regression diagnostics revealed the same potential outlier. In addition, the area under the ROC curve was similar to the initial model and thus, the exploratory baseline model was good at discriminating between patients who did and who did not develop thrombocytopenia. Therefore, the exploratory model produced was similar to the initial baseline model, and the new variable yielded no additional benefit.

4.4.2 Exploratory ICU/CCU model

The exploratory ICU/CCU model differed slightly from the initial ICU/CCU model following the inclusion of bleeding episodes as a potential candidate variable. Changes in the exploratory model included the following (Table 22): bleeding episodes was identified as an independent risk indicator, with an odds ratio for thrombocytopenia of 3.24; PRBC transfusions no longer appeared as a risk indicator for thrombocytopenia, but was replaced by bleeding episodes; and a new risk indicator appeared, medication class inotropes, which had been a borderline variable during the development of the initial ICU/CCU model. The appearance of class inotropes as an independent risk indicator in the exploratory ICU/CCU model increased the number of risk indicators from 9 to 10. Inotropes are administered to patients who are hemodynamically unstable, require pharmacologic support of the failing circulation (Notterman, 1991), and thus, inotropes are also indicators of severity of illness. These drugs have also been reported to inhibit platelet function and possibly cause transient thrombocytopenia (Notterman, 1991). The exploratory ICU/CCU model was a better fit of the data, as demonstrated by a modest increase in sensitivity (54.4% as compared to 51.5%) and a high p-value ($p = 0.59$) for the Hosmer-Lemeshow Goodness of Fit test. Small increases in the –2 log-likelihood, Pearson's r^2, and ROC curve indicated that this model correctly identifies a few more patients who actually did develop thrombocytopenia. The inclusion of a new variable for bleeding episodes did convey slightly more information about the study patients, but overall the increase in information was small.

4.5 CLINICAL OUTCOMES

Hemorrhagic manifestations have been reported in patients who have developed thrombocytopenia (Easton, 1984), however the platelet count is usually less than 20×10^9/L (Lind, 1995; Williams, 1995) in patients who have an overt bleeding episode. In the present study, only 2 of 68 patients (3%) who met the criteria for thrombocytopenia subsequently hemorrhaged. These patients had minimum platelet counts of 140×10^9/L and 106×10^9/L respectively, prior to the bleeding episodes. The lowest platelet count recorded among the 68 thrombocytopenic patients was 42×10^9/L. Thus, it is likely that the infrequent occurrence of hemorrhagic manifestations following the development of thrombocytopenia was partly due to the fact that no patients had platelet counts below 20×10^9/L.

The duration of ICU/CCU and hospital stays, as well as mortality rate, were all greater among patients who experienced thrombocytopenia (Table 25). Several previous studies have also reported similar findings (Baughman et al., 1993; Hanes et al., 1997; Cawley et al., 1999; Stephan et al., 1999). Thrombocytopenia can directly increase mortality if it results in hemorrhage or leads to thrombosis secondary to HIT. Since hemorrhage was infrequent among thrombocytopenic patients in this study, and since the incidence of HIT is considered to be quite low (1% to 3%) (Greinacher, 1995; Warkentin et al., 1995; Warkentin et al., 1998), it is unlikely that the increased mortality was caused by the occurrence of thrombocytopenia. Moreover, in the absence of bleeding, thrombosis, or profound thrombocytopenia (i.e. $< 20 \times 10^9$/L), it is unlikely that clinicians would keep patients in the ICU/CCU simply because of a platelet count below 150×10^9/L. Both the baseline and ICU/CCU logistic regression models identified variables that were indicative of severity of illness that were associated with thrombocytopenia. It is therefore likely that the greater duration of ICU/CCU and hospital stay and mortality among thrombocytopenic patients were related to their greater severity of illness.

In the ICU/CCU setting, many patients receive heparin. When thrombocytopenia occurs, clinicians become concerned about the development of HIT, as it is associated with an increased risk of limb- or life-threatening thrombosis (Greinacher, 1995; Warkentin *et al.*, 1995; Warkentin *et al.*, 1998). As a result, heparin therapy is often discontinued when patients develop thrombocytopenia (Bonfiglio *et al.*, 1995). Although heparin was not identified as an independent risk indicator following multivariate

analysis, physicians discontinued heparin therapy in 10 of 57 patients (18%) who developed thrombocytopenia in the present study. In addition, it is important to note that no patient who exhibited thrombocytopenia after 5 or more days of heparin therapy developed a thrombotic episode. To avoid unnecessary heparin discontinuation and associated thrombotic risk, it would be useful for clinicians to have an understanding of non-heparin related patient variables associated with a high probability of developing thrombocytopenia. In future, it may be possible for clinicians to use a logistic regression model for thrombocytopenia, in conjunction with clinical laboratory tests for heparin-dependent antiplatelet antibodies, to make better informed decisions about heparin therapy in patients who develop thrombocytopenia.

5 CONCLUSIONS AND IMPLICATIONS FOR FUTURE RESEARCH

The present investigation was the first large, prospective designed study to identify risk indicators for thrombocytopenia in a community-based ICU/CCU. The observed incidence of thrombocytopenia was 18.8% (95% CI: 14.8% - 22.8%), with a higher incidence in intensive care patients (30%, 95% CI: 24% - 38%) than coronary care patients (8%, 95% CI: 4% - 12%).

Risk indicators identified by the baseline model as being independently associated with the development of thrombocytopenia included: platelet count on admission, the patient's age, severity of illness (APACHE II score), and several diagnoses (sepsis, gastrointestinal, respiratory non-surgery, musculoskeletal/connective tissue, and GI bleed). Multivariate logistic regression modelling identified admission platelet count, Swan-Ganz catheter insertion, ASA, FFP and PRBC transfusions, and sepsis gastrointestinal, respiratory non-surgery, and musculoskeletal/connective tissue diagnosis as risk indicators associated with thrombocytopenia during a patient's ICU/CCU stay. The ICU/CCU model was found to have increased sensitivity compared to the baseline model, and included additional variables: FFP and PRBC transfusions, and Swan-Ganz catheter insertion. Overall, the risk indicators identified are consistent with findings reported in a variety of other settings. Markers for severity of illness (sepsis, APACHE II score, or respiratory non-surgery diagnosis) and foreign surfaces (Swan-Ganz catheters, or arterial or central lines) appeared to be associated with the development of thrombocytopenia in these patients. Moreover, markers for bleeding were noted to be possible risk indicators for thrombocytopenia. Bleeding episodes are not often noted in literature as being causally associated with thrombocytopenia, and this issue warrants further investigation. Another important finding was that no specific drug therapy was identified as being associated with the development of thrombocytopenia, with the exception of a small protective effect of ASA in the ICU/CCU model. In particular, no effect of heparin therapy was observed in the multivariate logistic regression model. However, clinicians frequently discontinue heparin, apparently because of a perceived risk of patients developing HIT-related thrombosis. Future research involving the use of logistic regression models, such as those developed in the present study, might enable clinicians to identify patients at highest risk for non-heparin related thrombocytopenia. This

information may prove clinically useful in making decisions about continuing or discontinuing heparin therapy.

Given the differences in thrombocytopenia between ICU and CCU patients, a larger set of patients will allow the development of a model in coronary care patients, as some of the risk indicators identified by the baseline and ICU/CCU models are likely to be different in intensive and coronary care patients.

The best way to evaluate predictive models is to investigate how well they estimate risk for the outcome variable in future groups of patients. Therefore, validation studies should be performed with both the baseline and ICU/CCU models to further investigate their discriminative performance. It has been noted that if the number of candidate variables used in developing a multivariate model is greater than 10 times the number of occurrences of the binary outcome in the least frequent group, there is a risk that the model may be overfitted (Harrell *et al.*, 1996; Harrell *et al.*, 1985). Overfitting the model can adversely affect its' discrimination in a validation study on a new data set. Therefore, for future validation studies, it may be necessary to revise the baseline and ICU/CCU models using appropriate data reduction techniques.

Also consistent with other studies was the observation that patients in the ICU/CCU setting who developed thrombocytopenia had longer ICU/CCU and hospital stays and higher morbidity and mortality. However, it appears likely from the results of the present study that thrombocytopenia was a marker for severity of illness, rather than being a cause of increased ICU/CCU and hospital stay or mortality.

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APPENDIX 3

DATA BASE WORKSHEETS

PATIENT DEMOGRAPHICS

Patient Name:_____ MRN:_____ Study Number:_____

ICU/CCU Bed Number:_____ PHN:_____

Age: _____ Date of Birth:_____

Gender: M / F

Race: _____

APACHE II Score: _____

Alcohol History:_____

Date Admitted to ICU/CCU: _____ Where did patient come from: ER, WARD, OTHER

HOSP Duration of ICU/CCU Stay Before Thrombocytopenia: _____

Total Duration of Stay in the ICU/CCU:_____/Total Stay in Hospital_____

Weight:_____ Height:_____

LABORATORY VALUES:

DATE	TIME	HEMOGLOBIN	PLATELETS	RENAL DYSFUNCTION		HEPATIC DYSFUNCTION					
				S Cre	Cre Cl	AST	ALT	ALK	TotBil	DirBil	INR

Admission platelet count:_____

Did the patient develop thrombocytopenia:_____ If yes, what was the count:_____

Date:_____

Platelet count: minimum:_____ mean:_____ threshold:_____

Hemoglobin: minimum:_____ mean:_____

Appendix 3 continued

MEDICATIONS PRIOR AND DURING ICU/CCU STAY PRIOR TO THROMBOCYTOPENIA:

N.B. RECORD ALL MEDICATIONS IF NO THROMBOCYTOPENIA

N.B. ONLY RECORD MEDICATIONS TAKEN FOR THE PAST 3 MONTHS.

MEDICATIONS	✓	PAST USE	START/STOP DATE	MEDICATIONS	✓	PAST USE	START/STOP DATE
ACETAZOLAMIDE				FUROSEMIDE			
ACETOHEXAMIDE				GENTAMICIN			
ALDACTHIAZIDE				GLICLAZIDE			
AMIKACIN				GLYBURIDE			
AMOXICILLIN				HYDROCHLOROTHIAZIDE			
AMPHOTERICIN B				IBUPROFEN			
AMPICILLIN				IMIPENEM			
AMRINONE				INDOMETHICIN			
ANTINEOPLASTIC AGENT				IPRATROPIUM BR			
ASA				ISOPROTERENOL			
AURANOFIN (PO)				KETOCONAZOLE			
AUROTHIANALATE (IV)				KETOPROFEN			
AZOGANTRIZIN				MEFENAMIC ACID			
CEFACLOR				METHYLDOPA			
CEFAMANDOLE				METOLAZONE			
CEFAZOLIN				NAPROXEN			
CEFOTAXIME				NOREPINEPHRINE			
CEFTAZIDIME				OLSALAZINE			
CEFTIZOXIME				PENICILLIN G			
CEFTRIAXONE				PENICILLIN V			
CEFUROXIME				PHENYLEPHRINE			
CEPHALEXIN				PHENYTOIN			
CHLORPROPAMIDE				PIPERACILLIN			
CHLORTHALIDONE				QUINIDINE			
CIMETIDINE				QUININE			
CLOXACILLIN				RANITIDINE			
COTRIMOXAZOLE				SALBUTAMOL			
DICLOFENAC				SULFADIAZINE			
DIGOXIN				SULFASALAZINE			
DOBUTAMINE				SULFINPYRAZONE			
DOPAMINE				SULFISOXAZOLE			
DYAZIDE				TICARCILLIN			
EPINEPHRINE				TINZAPARIN			
ETHACRYNIC ACID				TOBRAMYCIN			
FLUCONAZOLE				TOLBUTAMIDE			
FLUCYTOSINE				VANCOMYCIN			

Total number of medications patients exposed to prior to thrombocytopenia during ICU/CCU stay:_____

Total number of medications if patient does not develop thrombocytopenia during ICU/CCU stay:_____

Appendix 3 continued

HEPARIN

Date heparin first started:_____ Platelet count when heparin first started:_____

DATE	MEAN DOSE/ROUTE	DURATION	INDICATION

Did the patient ever receive heparin in the past:_____ If yes, when:_____

Was heparin discontinued as a result of thrombocytopenia:_____

Days patient on heparin:_____

DOSE RANGE	TOTAL HEPARIN DOSE
FULL ANTICOAGULATION FOR THROMBOSIS HERAPY:15,000U/DAY	
PROPHYLACTIC DOSES: 10,000 - 15,000 U/DAY	
DOSES TO MAINTAIN IV LINE PATENCY AND PULMONARY ARTERY CATHETERS: < 10,000 U/DAY	

Dose heparin per day:_____

CATHETER TYPE	START/STOP DATE	UNITS OF HEPARIN
SWAN GANZ (PA)		
ARTERIAL LINE		
CVP LINE		

Infusion Rate: 6U/hr (144U/d) Include 100U/24hrs for flushes

ELISA TEST:

Is the test performed on this patient:_____

If yes, is the test for early, late, or no thrombocytopenia, but patient on heparin:_____

A_{492nm} value:_____

Result:_____

Appendix 3 continued

DIAGNOSES:

Diagnosis at thrombocytopenia or discharge:

DIAGNOSES	YES/NO	DIAGNOSES	YES/NO
ACUTE MYOCARDIAL INFARCTION		KIDNEY, URINARY TRACT, REPRODUCTIVE	
CARDIOVASCULAR SURGERIES		MALIGNANCY	
CARDIOVASCULAR NONSURGERIES		MUSCULOSKELETAL & CONNECTIVE TISSUE	
DIABETES MELLITUS		NERVOUS SYSTEM	
DRUG OVERDOSE/POISONINGS		RESPIRATORY NONSURGICAL	
ENDOCRINE AND NUTRITION		RESPIRATORY SURGICAL	
GASTROINTESTINAL		SEPSIS	
GI BLEED		UNSTABLE ANGINA	
INFECTION			

Admitting Diagnosis:

PROCEDURES:

PROCEDURES	PRIOR TO ICU/CCU	DURING ICU/CCU	START DATE
PULMONARY ARTERY CATHETER PLACEMENT			
TRANSFUSIONS (TOT. NUMBER AND VOLUME)			
PACKED RED BLOOD CELLS			
FRESH FROZEN PLASMA			
PLATELETS			
CARDIAC VALVES OR PROSTHESIS			
SURGICAL PROCEDURES (ALL)			
MECHANICAL VENTILATION			
CARDIOPULMONARY BYPASS SURGERY		X	X

Surgical Procedure(s):

FINAL CLINICAL OUTCOME:

Transfer from ICU/CCU: _____

Discharge from ICU/CCU: _____

Expired: _____ Did patient expire on ward after leaving the ICU/CCU: _____

EVENT	YES/NO	DATE
THROMBOEMBOLISM		
HEMORRHAGE		
SKIN ERUPTION		

Appendix 3 continued

APACHE II SCORE

THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature-rectal (°C)	O ≥ 41°	O 39°-40.9°		O 38.5°-38.9°	O 36°-38.4°	O 34°-35.9°	O 32°-33.9°	O 30°-31.9°	O ≤29.9°
Mean Arterial Pressure (mm Hg)	O ≥ 160	O 130-159	O 110-129		O 70-109		O 50-69		O ≤ 49
Heart Rate (ventricular response)	O ≥ 180	O 140-179	O 110-139		O 70-109		O 55-69	O 40-54	O ≤ 39
Respiratory Rate (non-ventilated or ventilated)	O ≥ 50	O 35-49		O 25-34	O 12-24	O 10-11	O 6-9		O ≤ 5
Oxygenation: A-a DO_2 or PaO_2 (mm Hg) a) FiO_2 ≥0.5 record A-a DO_2	O ≥ 500	O 350-499	O 200-349		O ≤ 200				
b) FiO_2 < 0.5 record only PaO_2					O PO_2 > 70	O PO_2 51-70		O PO_2 55-60	O PO_2 <55
Arterial pH	O ≥ 7.7	O 7.6-7.69		O 7.5-7.59	O 7.33-7.49		O 7.25-7.32	O 7.15-7.24	O < 7.15
Serum Sodium (mMol/L)	O ≥ 180	O 160-179	O 155-159	O 150-154	O 130-149		O 120-129	O 111-119	O ≤ 110
Serum Potassium (mMol/L)	O ≥ 7	O 6-6.9		O 5.5-5.9	O 3.5-5.4	O 3-3.4	O 2.5-2.9		O < 2.5
Serum Creatinine (mg/100mL) (Double point score for acute renal failure)	O ≥ 3.5	O 2-3.4	O 1.5-1.9		O 0.6-1.4		O < 0.6		
Hematocrit (%)	O ≥ 60		O 50-59.9	O 46-49.9	O 30-45.9		O 20-29.9		O < 20
White Blood Count (total/mm^3) (in 1000s)	O ≥ 40		O 20-39.9	O 15-19.9	O 3-14.9		O 1-2.9		O < 1
Glasgow Coma Scale (GCS) Score = 15 minus actual GCS									
A) Total Acute Physiology Score (APS)—sum of the 12 individual variable points									
Serum HCO_3 (venous—m<ol/L) [Not preferred; use if no ABGs)	O ≥ 52	O 41-51.9		O 32-40.9	O 22-31.9		O 18-21.9	O 15-17.9	O < 15

B) AGE POINTS:

Assign points to age as follows:

AGE (yrs)	Points
≤ 44	0
45 – 54	2
55 – 64	3
65 – 74	4
≥ 75	5

C) CHRONIC HEALTH POINTS

If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:

a.) for non-operative or emergency postoperative patients—5 points

or

b.) for elective postoperative patients—2 points

Calculate the following ≤ 24 hrs after ICU admission:

1. $MAP = \frac{2\,(DBP) + SBP}{3}$

2. $A\text{-}a\ DO_2 = 713\,(FiO_2) - \frac{P_aCO_2}{0.8} - P_aO_2$

3. $SCr\ (mg/100mL) = \frac{SCr\ (\mu mol/L)}{88.40}$

NET APACHE II SCORE:_____

APPENDIX 4

UNIVARIATE ANALYSIS

Univariate Analysis of Patient Characteristics

Potential Risk Indicator	TCP[a] (N = 68)	No TCP[a] (N = 294)	p-Value[b]
Gender Male	40 (58.8%)	189 (64.3%)	0.709
Age	**60.3 ± 18.2**	**63.9 ± 14.6**	**0.081**
APACHE II Score	**21.3 ± 11.6**	**14.1 ± 8.2**	**< 0.001**
Acute Physiology Score	**17.5 ± 10.8**	**9.9 ± 7.7**	**< 0.001**
History of Alcohol Use	**14 (20.6%)**	**27 (9.2%)**	**0.007**
Ethnic Origin Caucasian	60 (88.2%)	257 (87.4%)	0.853
Weight	76.9 ± 18.6	76.0 ± 16.8	0.690

[a]Values indicate either the number (percentage) of patients (dichotomous data) or the mean ± SD (continuous data)

[b]Univariate analysis by chi-square test (dichotomous data) or Wald's test (continuous data)

Appendix 4 continued

Univariate Analysis of Medications Administered

Potential Risk Indicator	TCP[a] (N = 68)	No TCP[a] (N = 294)	p-Value[b]
Acetazolamide	1 (1.5%)	13 (4.4%)	0.255
Ampicillin	2 (2.9%)	10 (3.4%)	0.849
Antineoplastic Agents	0	2 (0.7%)	0.495
Acetylsalicylic acid	**14 (20.6%)**	**154 (52.4%)**	**< 0.001**
Cefotaxime	4 (5.9%)	14 (4.8%)	0.702
Cefazolin	**8 (11.8%)**	**22 (7.5%)**	**0.248**
Ceftazidime	2 (2.9%)	4 (1.4%)	0.358
Ceftizoxime	**8 (11.8%)**	**14 (4.8%)**	**0.029**
Cefuroxime	12 (17.6%)	43 (14.6%)	0.532
Cimetidine	0	3 (1.0%)	0.403
Cloxacillin	3 (4.4%)	12 (4.1%)	0.902
Cotrimoxazole	0	9 (3.1%)	0.144
Diclofenac	0	2 (0.7%)	0.495
Digoxin	9 (13.2%)	49 (16.7%)	0.487
Dobutamine	2 (2.9%)	5 (1.7%)	0.503
Dopamine	**27 (39.7%)**	**44 (15.0%)**	**< 0.001**
Epinephrine	2 (2.9%)	13 (4.4%)	0.581
Fluconazole	1 (1.5%)	2 (0.7%)	0.517
Furosemide	30 (44.1%)	129 (43.9%)	0.971
Gentimicin	5 (7.4%)	19 (6.5%)	0.790
Glyburide	2 (2.9%)	14 (4.8%)	0.510
Heparin	57 (83.8%)	249 (84.7%)	0.858
Hydrochlorothiazide	1 (1.5%)	10 (3.4%)	0.403
Imipenem	**8 (11.8%)**	**7 (2.4%)**	**< 0.001**
Ipratropium Bromide	**38 (55.9%)**	**93 (31.6%)**	**< 0.001**
Metolazone	2 (2.9%)	10 (3.4%)	0.849
Naproxen	0	2 (0.7%)	0.495
Norepinephrine	**10 (14.7%)**	**9 (3.1%)**	**< 0.001**
Penicillin G	1 (1.5%)	3 (1.0%)	0.749
Phenytoin	3 (4.4%)	7 (2.4%)	0.357
Quinidine	0	1 (0.3%)	0.630
Quinine	0	2 (0.6%)	0.495
Rantidine	**29 (42.6%)**	**63 (21.4%)**	**< 0.001**
Salbutamol	**39 (57.4%)**	**104 (35.4%)**	**0.001**
Tinzaparin	**1 (1.5%)**	**15 (5.1%)**	**0.189**
Vancomycin	2 (2.9%)	1 (0.3%)	0.033

Appendix 4 continued

Univariate Analysis of Medication Classes

Potential Risk Indicator	TCP[a] (N = 68)	No TCP[a] (N = 294)	p-Value[b]
Inotropes	**30 (44.1%)**	**47 (16.0%)**	**< 0.001**
Cephalosporins	**32 (47.1%)**	**90 (30.6%)**	**0.010**
Penicillins	5 (7.4%)	21 (7.1%)	0.952
H_2-Antagonists	**29 (42.6%)**	**66 (22.4%)**	**0.001**
Sulfa Medications	31 (45.6%)	138 (46.9%)	0.841

Univariate Analysis of Heparin Therapy

Potential Risk Indicator	TCP[a] (N = 68)	No TCP[a] (N = 294)	p-Value[b]
Heparin within past 8 Weeks	6 (8.8%)	22 (7.5%)	0.709
Low Dose Heparin[c]	7 (10.3%)	20 (6.8%)	0.323
Medium Dose Heparin[c]	34 (50.0%)	90 (30.6%)	0.002
High Dose Heparin[c]	16 (23.5%)	139 (47.3%)	< 0.001
Duration Heparin Therapy	2.9 ± 4.5	3.7 ± 5.2	0.265
Total Cumulative Heparin Dose	39479.0 ± 64011.9	68967.2 ± 119060.1	0.049
Heparin Dose/Day	**10938.6 ± 9979.1**	**16739.6 ± 12789.0**	**0.001**

[c] Low dose heparin = < 1000 Units/day; Medium dose heparin = 1000 - 16000 Units/day; High dose heparin = > 16000 Units/day

Appendix 4 continued

Univariate Analysis of Most Responsible Diagnosis

Potential Risk Indicator	TCP[a] (N = 68)	No TCP[a] (N = 294)	p-Value[b]
Acute Myocardial Infarction	**8 (11.8%)**	**90 (30.6%)**	**0.002**
Cardiovascular Nonsurgery	8 (11.8%)	48 (16.3%)	0.349
Drug Overdose/Poisoning	3 (4.4%)	10 (3.4%)	0.687
Gastrointestinal	**6 (8.8%)**	**9 (3.1%)**	**0.032**
Gastrointestinal Bleed	**4 (5.9%)**	**6 (2.0%)**	**0.082**
Infection	**1 (1.5%)**	**16 (5.4%)**	**0.163**
Musculoskeletal/Connective Tissue	**7 (10.3%)**	**5 (1.7%)**	**< 0.001**
Nervous System	**5 (7.4%)**	**9 (3.1%)**	**0.098**
Respiratory Nonsurgery	**17 (25.0%)**	**35 (11.9%)**	**0.006**
Respiratory Surgery	1 (1.5%)	10 (3.4%)	0.403
Sepsis	**7 (10.3%)**	**6 (2.0%)**	**0.001**
Unstable Angina	**1 (1.5%)**	**35 (11.9%)**	**0.010**
ICU Most Responsible Diagnosis	51 (75%)	114 (38.8%)	< 0.001

Univariate Analysis of Procedures

Potential Risk Indicator	TCP[a] (N = 68)	No TCP[a] (N = 294)	p-Value[b]
Surgery Past 24 Hours	**19 (27.9%)**	**53 (18.0%)**	**0.065**
Swan Ganz Catheter	**33 (48.5%)**	**31 (10.9%)**	**< 0.001**
PRBC Transfusion	**18 (26.5%)**	**20 (6.8%)**	**< 0.001**
FFP Transfusion	**6 (8.8%)**	**3 (1.0%)**	**< 0.001**
Surgical Procedures	7 (10.3%)	43 (14.6%)	0.351
Mechanical Ventilation	**37 (54.4%)**	**60 (20.4%)**	**< 0.001**

Univariate Analysis of Organ Dysfunction

Potential Risk Indicator	TCP[a] (N = 68)	No TCP[a] (N = 294)	p-Value[b]
Renal Dysfunction	7 (10.3%)	35 (11.9%)	0.709
Hepatic Dysfunction	**6 (8.8%)**	**6 (2.0%)**	**0.005**

Appendix 4 continued

Univariate Analysis of Laboratory Indices

Potential Risk Indicator	**TCP[a] (N = 68)**	**No TCP[a] (N = 294)**	**p-Value[b]**
Admission Platelet Count	**216.1 ± 65.7**	**253.2 ± 79.7**	**< 0.001**
Mean Platelet Count	159.3 ± 28.8	243.7 ± 79.0	< 0.001
Minimum Platelet Count	110.7 ± 25.9	211.6 ± 69.3	< 0.001
Mean Hemoglobin Concentration	113.2 ± 21.4	121.8 ± 20.0	0.001
Minimum Hemoglobin Concentration	**103.1 ± 23.9**	**114.3 ± 22.2**	**< 0.001**

APPENDIX 5

SPSS PRINTOUT OF STEPWISE BACKWARD MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF THE ICU/CCU MODEL

(FIRST, SECOND, AND LAST STEPS SHOWN BELOW)

```
Total number of cases:      362 (Unweighted)
Number of selected cases:   362
Number of unselected cases: 0

Number of selected cases:                    362
Number rejected because of missing data:     0
Number of cases included in the analysis:    362

Dependent Variable Encoding:
Original        Internal
Value           Value
       0        0
       1        1

Dependent Variable..   DIDTCPDE   DidTCPDevelop

Beginning Block Number  0.  Initial Log Likelihood Function
-2 Log Likelihood   349.75246

* Constant is included in the model.

Estimation terminated at iteration number 3 because
Log Likelihood decreased by less than .01 percent.

Classification Table for DIDTCPDE
The Cut Value is .50
                  Predicted
                  0         1      Percent Correct
                   0 |       1
                     |
Observed             |
                     |
   0      0      294 |       0      100.00%
                     |
   1      1       68 |       0        .00%
                     |
                     |
                     |  Overall     81.22%

---------------- Variables in the Equation -----------------
Variable            B        S.E.      Wald     df       Sig        R
Constant      -1.4640       .1346 118.3739      1     .0000

                          95% CI for Exp(B)
Variable       Exp(B)      Lower      Upper
```

Appendix 5 continued

Beginning Block Number 1. Method: Backward Stepwise (LR)

Variable(s) Entered on Step Number

1..	ACUTEMYO	AcuteMyocardialInfarction
	ADMISS50	Admission Platelet Count divided by 50
	AGE	aGE
	ALCOHOLH	AlcoholHistory
	APACHEII	APACHEIIScore
	ASA	Acetyl salicylic acid (ASA)
	FFPTRSYN	FFPTransfusions Yes or No
	GASTROIN	Gastrointestinal
	GIBLEED	GI Bleed
	HEPARID2	HeparinDose/DayWithNoZeroDose
	IMIPENEM	IMIPENEM
	INFECTIO	Infection
	LIVERDYS	HepaticDysfunction
	MUSCULOS	Musculoskeletal&ConnTissue
	RESNOSUR	RespiratoryNonsurgery
	SALBUTAM	Salbutamol
	SEPSIS	Sepsis
	SURGBFIC	SurgicalProceduresPast
	TRAPRBCY	PRBCTransfusionsYes
	UNSTABLE	UnstableAngina
	CLINOTRO	Class Inotropes (3)
	CLCEPHAL	Class Cephalosporins (6)
	CLH2ANTA	Class H2-Antagonists (2)
	NERVOUSS	NervousSystem
	SWANGANZ	SwanGanzCatheter

Estimation terminated at iteration number 5 because
Log Likelihood decreased by less than .01 percent.

-2 Log Likelihood	216.441
Goodness of Fit	891.813
Cox & Snell - R^2	.308
Nagelkerke - R^2	.497

	Chi-Square	df	Significance
Model	133.312	25	.0000
Block	133.312	25	.0000
Step	133.312	25	.0000

Appendix 5 continued

---------- Hosmer and Lemeshow Goodness-of-Fit Test----------

	DIDTCPDE = 0		DIDTCPDE = 1		
Group	Observed	Expected	Observed	Expected	Total
1	35.000	35.919	1.000	.081	36.000
2	36.000	35.590	.000	.410	36.000
3	36.000	35.144	.000	.856	36.000
4	36.000	34.542	.000	1.458	36.000
5	34.000	33.801	2.000	2.199	36.000
6	35.000	32.801	1.000	3.199	36.000
7	26.000	31.126	10.000	4.874	36.000
8	26.000	27.115	10.000	8.885	36.000
9	25.000	20.095	11.000	15.905	36.000
10	5.000	7.863	33.000	30.137	38.000

	Chi-Square	df	Significance
Goodness-of-fit test	25.4259	8	.0013

Classification Table for DIDTCPDE
The Cut Value is .50

		Predicted 0	Predicted 1	Percent Correct
Observed		0	1	
0	0	281	13	95.58%
1	1	32	36	52.94%
			Overall	87.57%

---------- Variables in the Equation ----------

Variable	B	S.E.	Wald	df	Sig	R
ACUTEMYO	.5079	.7445	.4654	1	.4951	.0000
ADMISS50	-.9845	.2161	20.7561	1	.0000	-.2316
AGE	-.0165	.0121	1.8490	1	.1739	.0000
ALCOHOLH	.3747	.5168	.5257	1	.4684	.0000
APACHEII	.0169	.0286	.3499	1	.5542	.0000
ASA	-.7761	.5925	1.7159	1	.1902	.0000
FFPTRSYN	3.2854	1.3066	6.3221	1	.0119	.1112
GASTROIN	1.4930	.8581	3.0272	1	.0819	.0542
GIBLEED	.6128	1.2111	.2560	1	.6129	.0000
HEPARID2	-7.4E-06	1.988E-05	.1368	1	.7114	.0000
IMIPENEM	.9449	.9253	1.0430	1	.3071	.0000
INFECTIO	.1139	1.2468	.0083	1	.9272	.0000
LIVERDYS	-.5385	1.0893	.2443	1	.6211	.0000
MUSCULOS	2.4215	.8065	9.0144	1	.0027	.1416
RESNOSUR	1.0697	.5783	3.4222	1	.0643	.0638
SALBUTAM	-.4775	.5161	.8561	1	.3548	.0000
SEPSIS	2.7431	.8858	9.5908	1	.0020	.1473
SURGBFIC	.0016	.4825	.0000	1	.9973	.0000

Appendix 5 continued

Variable	B	S.E.	Wald	df	Sig	R
TRAPRBCY	.4629	.6178	.5613	1	.4537	.0000
UNSTABLE	-.5385	1.1788	.2087	1	.6478	.0000
CLINOTRO	.8382	.5393	2.4159	1	.1201	.0345
CLCEPHAL	-.0968	.4541	.0454	1	.8312	.0000
CLH2ANTA	-.1233	.4522	.0743	1	.7852	.0000
NERVOUSS	.5217	.8280	.3971	1	.5286	.0000
SWANGANZ	1.8497	.5473	11.4214	1	.0007	.1641
Constant	2.7005	1.2501	4.6664	1	.0308	

		95% CI for Exp(B)	
Variable	Exp(B)	Lower	Upper
ACUTEMYO	1.6618	.3862	7.1504
ADMISS50	.3736	.2446	.5707
AGE	.9836	.9605	1.0073
ALCOHOLH	1.4545	.5283	4.0049
APACHEII	1.0171	.9616	1.0758
ASA	.4602	.1441	1.4698
FFPTRSYN	26.7192	2.0635	345.9706
GASTROIN	4.4504	.8279	23.9232
GIBLEED	1.8457	.1719	19.8182
HEPARID2	1.0000	1.0000	1.0000
IMIPENEM	2.5726	.4196	15.7747
INFECTIO	1.1206	.0973	12.9032
LIVERDYS	.5836	.0690	4.9362
MUSCULOS	11.2631	2.3181	54.7244
RESNOSUR	2.9146	.9384	9.0532
SALBUTAM	.6203	.2256	1.7057
SEPSIS	15.5357	2.7376	88.1656
SURGBFIC	1.0016	.3890	2.5790
TRAPRBCY	1.5886	.4733	5.3318
UNSTABLE	.5837	.0579	5.8821
CLINOTRO	2.3123	.8035	6.6541
CLCEPHAL	.9078	.3728	2.2106
CLH2ANTA	.8840	.3644	2.1447
NERVOUSS	1.6850	.3325	8.5387
SWANGANZ	6.3582	2.1749	18.5876

---------- Model if Term Removed ----------

Term Removed	Log Likelihood	-2 Log LR	df	Significance of Log LR
ACUTEMYO	-108.458	.475	1	.4909
ADMISS50	-126.132	35.823	1	.0000
AGE	-109.150	1.859	1	.1728
ALCOHOLH	-108.477	.514	1	.4735
APACHEII	-108.396	.350	1	.5539
ASA	-109.095	1.750	1	.1859
FFPTRSYN	-112.334	8.228	1	.0041
GASTROIN	-109.695	2.949	1	.0859
GIBLEED	-108.345	.249	1	.6175
HEPARID2	-108.289	.138	1	.7104
IMIPENEM	-108.753	1.066	1	.3019

Appendix 5 continued

Term Removed	Log Likelihood	-2 Log LR	df	Significance of Log LR
INFECTIO	-108.225	.008	1	.9277
LIVERDYS	-108.343	.245	1	.6209
MUSCULOS	-112.681	8.921	1	.0028
RESNOSUR	-109.946	3.452	1	.0632
SALBUTAM	-108.659	.878	1	.3488
SEPSIS	-113.288	10.135	1	.0015
SURGBFIC	-108.220	.000	1	.9973
TRAPRBCY	-108.501	.561	1	.4540
UNSTABLE	-108.334	.228	1	.6332
CLINOTRO	-109.407	2.373	1	.1235
CLCEPHAL	-108.243	.046	1	.8309
CLH2ANTA	-108.258	.075	1	.7847
NERVOUSS	-108.417	.393	1	.5308
SWANGANZ	-114.381	12.321	1	.0004

Variable(s) Removed on Step Number
2. SURGBFIC SurgicalProceduresPast

Estimation terminated at iteration number 5 because
Log Likelihood decreased by less than .01 percent.

-2 Log Likelihood	216.441
Goodness of Fit	891.821
Cox & Snell - R^2	.308
Nagelkerke - R^2	.497

	Chi-Square	df	Significance
Model	133.312	24	.0000
Block	133.312	24	.0000
Step	.000	1	.9973

Note: A negative Chi-Square value indicates that the Chi-Square value has decreased from the previous step.

---------- Hosmer and Lemeshow Goodness-of-Fit Test----------

	DIDTCPDE = 0		DIDTCPDE = 1		
Group	Observed	Expected	Observed	Expected	Total
1	35.000	35.879	1.000	.121	36.000
2	36.000	35.509	.000	.491	36.000
3	36.000	34.999	.000	1.001	36.000
4	34.000	34.324	2.000	1.676	36.000
5	34.000	33.548	2.000	2.452	36.000
6	33.000	32.652	3.000	3.348	36.000
7	27.000	30.696	9.000	5.304	36.000
8	28.000	26.213	8.000	9.787	36.000
9	24.000	20.780	12.000	15.220	36.000
10	7.000	9.397	31.000	28.603	38.000

Appendix 5 continued

	Chi-Square	df	Significance
Goodness-of-fit test	13.6023	8	.0927

Classification Table for DIDTCPDE
The Cut Value is .50

		Predicted 0	Predicted 1	Percent Correct
Observed				
0	0	281	13	95.58%
1	1	32	36	52.94%
			Overall	87.57%

Variables in the Equation

Variable	B	S.E.	Wald	df	Sig	R
ACUTEMYO	.5077	.7414	.4689	1	.4935	.0000
ADMISS50	-.9845	.2160	20.7738	1	.0000	-.2317
AGE	-.0165	.0121	1.8641	1	.1722	.0000
ALCOHOLH	.3746	.5156	.5279	1	.4675	.0000
APACHEII	.0169	.0285	.3540	1	.5519	.0000
ASA	-.7763	.5896	1.7335	1	.1880	.0000
FFPTRSYN	3.2853	1.3067	6.3218	1	.0119	.1112
GASTROIN	1.4936	.8376	3.1802	1	.0745	.0581
GIBLEED	.6125	1.2057	.2580	1	.6115	.0000
HEPARID2	-7.4E-06	1.986E-05	.1370	1	.7113	.0000
IMIPENEM	.9453	.9181	1.0601	1	.3032	.0000
INFECTIO	.1132	1.2297	.0085	1	.9267	.0000
LIVERDYS	-.5390	1.0789	.2495	1	.6174	.0000
MUSCULOS	2.4214	.8049	9.0488	1	.0026	.1420
RESNOSUR	1.0696	.5762	3.4461	1	.0634	.0643
SALBUTAM	-.4774	.5156	.8573	1	.3545	.0000
SEPSIS	2.7430	.8852	9.6020	1	.0019	.1474
TRAPRBCY	.4634	.5942	.6082	1	.4355	.0000
UNSTABLE	-.5385	1.1787	.2087	1	.6478	.0000
CLINOTRO	.8383	.5392	2.4169	1	.1200	.0345
CLCEPHAL	-.0963	.4331	.0495	1	.8240	.0000
CLH2ANTA	-.1234	.4503	.0751	1	.7841	.0000
NERVOUSS	.5215	.8245	.4001	1	.5271	.0000
SWANGANZ	1.8497	.5473	11.4233	1	.0007	.1641
Constant	2.7008	1.2463	4.6964	1	.0302	

Appendix 5 continued

		95% CI for Exp(B)	
Variable	Exp(B)	Lower	Upper
ACUTEMYO	1.6614	.3885	7.1053
ADMISS50	.3736	.2447	.5706
AGE	.9837	.9606	1.0072
ALCOHOLH	1.4544	.5295	3.9950
APACHEII	1.0171	.9619	1.0754
ASA	.4601	.1449	1.4613
FFPTRSYN	26.7183	2.0634	345.9701
GASTROIN	4.4532	.8625	22.9937
GIBLEED	1.8450	.1737	19.6005
HEPARID2	1.0000	1.0000	1.0000
IMIPENEM	2.5736	.4256	15.5620
INFECTIO	1.1198	.1006	12.4710
LIVERDYS	.5833	.0704	4.8342
MUSCULOS	11.2612	2.3250	54.5447
RESNOSUR	2.9142	.9421	9.0146
SALBUTAM	.6204	.2258	1.7044
SEPSIS	15.5341	2.7402	88.0608
TRAPRBCY	1.5895	.4959	5.0943
UNSTABLE	.5836	.0579	5.8814
CLINOTRO	2.3124	.8037	6.6531
CLCEPHAL	.9082	.3886	2.1223
CLH2ANTA	.8839	.3657	2.1365
NERVOUSS	1.6845	.3347	8.4776
SWANGANZ	6.3580	2.1751	18.5853

---------- Model if Term Removed ----------

Term Removed	Log Likelihood	-2 Log LR	df	Significance of Log LR
ACUTEMYO	-108.459	.478	1	.4895
ADMISS50	-126.144	35.847	1	.0000
AGE	-109.155	1.869	1	.1715
ALCOHOLH	-108.478	.516	1	.4725
APACHEII	-108.398	.354	1	.5518
ASA	-109.107	1.773	1	.1830
FFPTRSYN	-112.347	8.252	1	.0041
GASTROIN	-109.764	3.086	1	.0790
GIBLEED	-108.346	.251	1	.6162
HEPARID2	-108.289	.138	1	.7103
IMIPENEM	-108.762	1.082	1	.2982
INFECTIO	-108.225	.008	1	.9272
LIVERDYS	-108.345	.249	1	.6175
MUSCULOS	-112.691	8.941	1	.0028
RESNOSUR	-109.961	3.481	1	.0621
SALBUTAM	-108.660	.879	1	.3485
SEPSIS	-113.293	10.146	1	.0014
TRAPRBCY	-108.523	.605	1	.4368
UNSTABLE	-108.334	.228	1	.6332
CLINOTRO	-109.408	2.374	1	.1234
CLCEPHAL	-108.245	.050	1	.8236
CLH2ANTA	-108.258	.075	1	.7835

Appendix 5 continued

Term Removed	Log Likelihood	-2 Log LR	df	Significance of Log LR
NERVOUSS	-108.418	.396	1	.5293
SWANGANZ	-114.382	12.323	1	.0004

Variable(s) Removed on Step Number
17.. CLINOTRO Class Inotropes (3)

Estimation terminated at iteration number 5 because
Log Likelihood decreased by less than .01 percent.

-2 Log Likelihood	226.190
Goodness of Fit	426.075
Cox & Snell - R^2	.289
Nagelkerke - R^2	.467

	Chi-Square	df	Significance
Model	123.563	9	.0000
Block	123.563	9	.0000
Step	-2.368	1	.1238

Note: A negative Chi-Square value indicates that the Chi-Square value has decreased from the previous step.

---------- Hosmer and Lemeshow Goodness-of-Fit Test----------

	DIDTCPDE = 0		DIDTCPDE = 1		
Group	Observed	Expected	Observed	Expected	Total
1	36.000	36.830	1.000	.170	37.000
2	36.000	35.312	.000	.688	36.000
3	36.000	34.689	.000	1.311	36.000
4	36.000	34.111	.000	1.889	36.000
5	33.000	33.371	3.000	2.629	36.000
6	29.000	32.111	7.000	3.889	36.000
7	32.000	30.890	5.000	6.110	37.000
8	28.000	26.233	8.000	9.767	36.000
9	19.000	20.771	17.000	15.229	36.000
10	9.000	9.682	27.000	26.318	36.000

	Chi-Square	df	Significance
Goodness-of-fit test	12.0924	8	.1471

Appendix 5 continued

Classification Table for DIDTCPDE
The Cut Value is .50

		Predicted 0	Predicted 1	Percent Correct
Observed				
0	0	281	13	95.58%
1	1	33	35	51.47%
			Overall	87.29%

---------- Variables in the Equation ----------

Variable	B	S.E.	Wald	df	Sig	R
ADMISS50	-.8543	.1865	20.9855	1	.0000	-.2330
ASA	-.8010	.3835	4.3613	1	.0368	-.0822
FFPTRSYN	2.9976	1.1717	6.5455	1	.0105	.1140
GASTROIN	1.4102	.6959	4.1060	1	.0427	.0776
MUSCULOS	2.2488	.6607	11.5842	1	.0007	.1655
RESNOSUR	.8419	.4611	3.3335	1	.0679	.0617
SEPSIS	2.7134	.8143	11.1039	1	.0009	.1613
TRAPRBCY	.9154	.5025	3.3185	1	.0685	.0614
SWANGANZ	2.1245	.3883	29.9324	1	.0000	.2826
Constant	1.4055	.7932	3.1398	1	.0764	

		95% CI for Exp(B)	
Variable	Exp(B)	Lower	Upper
ADMISS50	.4256	.2953	.6134
ASA	.4489	.2117	.9519
FFPTRSYN	20.0384	2.0162	199.1599
GASTROIN	4.0968	1.0473	16.0259
MUSCULOS	9.4763	2.5956	34.5973
RESNOSUR	2.3208	.9400	5.7301
SEPSIS	15.0805	3.0570	74.3941
TRAPRBCY	2.4977	.9329	6.6875
SWANGANZ	8.3685	3.9095	17.9135

---------- Model if Term Removed ----------

Term Removed	Log Likelihood	-2 Log LR	df	Significance of Log LR
ADMISS50	-130.045	33.900	1	.0000
ASA	-115.350	4.509	1	.0337
FFPTRSYN	-117.528	8.865	1	.0029
GASTROIN	-115.021	3.852	1	.0497
MUSCULOS	-118.711	11.233	1	.0008
RESNOSUR	-114.706	3.222	1	.0727
SEPSIS	-118.976	11.761	1	.0006
TRAPRBCY	-114.696	3.203	1	.0735
SWANGANZ	-128.817	31.443	1	.0000

Appendix 5 continued

---------- Variables not in the Equation ----------

Residual Chi Square not computed because of redundancies.

Variable	Score	df	Sig	R
ACUTEMYO	.3765	1	.5395	.0000
AGE	1.1170	1	.2906	.0000
ALCOHOLH	.5605	1	.4541	.0000
APACHEII	1.0890	1	.2967	.0000
GIBLEED	.1020	1	.7494	.0000
HEPARID2	.2285	1	.6326	.0000
IMIPENEM	1.2860	1	.2568	.0000
INFECTIO	.0129	1	.9097	.0000
LIVERDYS	.0177	1	.8941	.0000
SALBUTAM	.3329	1	.5639	.0000
SURGBFIC	.1777	1	.6733	.0000
UNSTABLE	.8923	1	.3449	.0000
CLINOTRO	2.4768	1	.1155	.0369
CLCEPHAL	.2203	1	.6388	.0000
CLH2ANTA	.0202	1	.8870	.0000
NERVOUSS	.5987	1	.4391	.0000

No more variables can be deleted or added.