BODY MASS INDEX AS A PREDICTOR OF MORBIDITY AND MORTALITY FOLLOWING LUNG TRANSPLANTATION

by

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A thesis submitted in conformity with the requirements for the Degree of Master of Science
Graduate Department of Nutritional Sciences
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Master of Science, 1999
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ABSTRACT

Limited data are available on the relationship between Body Mass Index (BMI) and morbidity and mortality in lung transplant populations. The objective of this study was to measure the association between post-transplant morbidity and mortality and preoperative BMI in end stage lung disease (ESLD). Dependent measures included Mortality at 90 days and 1 year post-transplantation; length of time in the Intensive Care Unit; length of time in the hospital; and, number of rejection episodes. Patients were grouped by BMI categories: <17 kg/m²; 17 to <20 kg/m²; 20 to 25 kg/m²; >25 to 27 kg/m²; and, >27 kg/m². The results indicated that patients with a pre-transplant BMI <17 kg/m² showed a trend to increased mortality following transplantation (p=0.085). Patient with a BMI >27 kg/m² had a significant increase in mortality (p=0.003). In conclusion, a pre-transplant BMI >27kg/m² was found to be a predictor of morbidity and mortality in ESLD patients post-transplantation.
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<tr>
<td>BMI</td>
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<td>EMP A1AD</td>
<td>Emphysema Alpha 1 Antitrypsin Deficiency</td>
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<td>ESLD</td>
<td>End Stage Lung Disease</td>
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<tr>
<td>FEV₁</td>
<td>Forced Expired Ventilation per Minute</td>
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<td>LOS(ICU)</td>
<td>Length of Stay in the Intensive Care Unit</td>
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<td>LOS(H)</td>
<td>Length of Stay in the Hospital</td>
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<td>MSOF</td>
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<td>OLTX</td>
<td>Orthotopic Liver Transplant</td>
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<td>SGA</td>
<td>Subjective Global Assessment</td>
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<td>Total Parenteral Nutrition</td>
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<td>Tx</td>
<td>Transplant</td>
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<td>TGH</td>
<td>Toronto General Hospital</td>
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INTRODUCTION

The first successful lung transplant in the world was performed in 1983 at the Toronto General Hospital (TGH). Since then, the University of Toronto, lung transplant program at the TGH has performed over 300 lung transplants. The number of patients with end stage lung disease (ESLD) being referred to the program for assessment for lung transplantation has steadily increased. There has been an increased number of potential candidates for lung transplantation, and an increased organ donor shortage. Thus, in order to optimize organ utilization it is imperative to identify patients with the best long-term survival potential. Nutritional status pre-transplantation may be an important component in making this decision.

A variety of nutrition parameters have been used to assess the nutritional status of patients. Some of these parameters have documented that a significant number of ESLD patients are malnourished. This is referred to as lung cachexia. It is also well documented that malnourished and/or obese surgical patients have increased morbidity and mortality postoperatively. While the majority of the research has been
conducted within the surgical domain, only two studies have examined nutritional status before lung transplantation and its effect on post-transplant mortality. These two studies have defined the rates of morbidity and mortality in patients outside the optimal Body Mass Index (BMI) range. Data on pre-transplant overweight/obesity and post lung transplant morbidity and/or mortality do not exist.

The purpose of this study was to measure, in the Toronto Hospital population, the relationship between BMI on morbidity and mortality following lung transplantation.
CHAPTER 1. REVIEW OF THE LITERATURE

1.1. NUTRITION ASSESSMENT TOOLS

Numerous techniques for evaluating the nutritional status of patients are available. Since the recognition of the need to develop tools to measure nutritional status by Blackburn in 1977, numerous nutrition parameters have been developed. One of the most popular of these is BMI.

1.1.1 BMI

There is a relationship between BMI values and morbidity and mortality in the general population. BMI values of 20-25 kg/m² represent a range associated with good health for most people. BMI values below 20 kg/m² and greater than 27 kg/m² can be associated with health problems. Obesity-related comorbidities are type 2 diabetes, hypertension, cardiovascular disease, and dyslipidemias. BMI has been recommended by the Expert Group on Weight Standards as the single most useful measure of weight status for the healthy Canadian adult aged 20 to 65 years. Ranges are often expressed to reflect a statistically derived best weight associated with the least
morbidity, mortality, and disease onset. The criteria for the ideal measure of weight in relation to morbidity and mortality data are the following: epidemiological validity, precision, reliability, accuracy, easy availability, special skills not required, low cost and acceptability by the client. BMI was selected as the primary weight index because it meets all of the above proposed criteria.\(^8\)

The American Dietetic Association (ADA) published a position paper in 1998, on weight management stating that BMI has become the medical standard used in defining weights.\(^9\) Healthy weights are associated with a BMI of 19 to 25 kg/m². While the ADA’s major focus was on obesity, they did recommend that nutritional intervention in patients outside these healthy weight ranges is critical.\(^9\)

BMI has been used in large scale studies. Durazo-Arizu reported on 13,242 participants in the NHANES I Epidemiologic study and found a relationship between BMI and mortality.\(^31\) While this study did not involve surgical or transplant patients, it did support the fact that BMI is being used as a useful marker to assess nutritional status.

Furthermore, studies using BMI as a marker of underweight
and overweight status have become widely utilized by such
groups as the Task Force on the treatment of Obesity,\textsuperscript{32}
Canadian Heart Health Research Group,\textsuperscript{33} and the Expert Panel
on the Identification, Evaluation and Treatment of Overweight in
Adults.\textsuperscript{34} BMI has also been studied in detail by the International
Dietary Energy Consultative Group of the Sub Committee on
Nutrition Task Force. BMI was recommended as an index to use
in defining adult chronic dietary energy deficiency.\textsuperscript{35} Values of
18.5, 17, and 16 kg/m\textsuperscript{2} are universally valid thresholds to
describe patients as mildly, moderately or severely energy
deficient (respectively) with only a 5% risk of error.\textsuperscript{36} A study by
Russell and colleagues demonstrated that BMI has become a
useful marker of nutritional status in the overweight population.\textsuperscript{37}
This study reported on reviewing the Year 2000 objective of
decreasing the prevalence of overweight and/or obesity in the
general population of United States. The sole outcome measure
of decreased prevalence will be determined using BMI. While
discussing the pathophysiology of obesity, Bray states that the
degree of obesity can be expressed in several ways;
nonetheless, BMI is the most useful marker.\textsuperscript{38} BMI is a valid
measure of adult nutritional status for the energy deficient and overweight, as well as, for individuals and communities.\cite{36}

Studies have used BMI as a nutrition assessment technique in medical, surgical, and transplant populations. Sixty-six percent of the patients admitted to either medical or surgical wards in a large teaching hospital were malnourished.\cite{39} Patients were classified as malnourished when BMI was $<20 \text{ kg/m}^2$ and as overweight when BMI was $>25 \text{ kg/m}^2$. A recent study of 3,607 hemodialysis patients showed BMI to be predictive of mortality in this patient population.\cite{40} There are two published studies using BMI as a nutrition assessment tool in the lung transplant population. Plochl et al indicated that for those patients who remained in the ICU longer than 5 days, a low BMI was a risk factor for ICU mortality.\cite{29} In a study examining the appropriate time to list Cystic Fibrosis (CF) patients for transplant, Snell et al found that patients with a BMI $<18 \text{ kg/m}^2$ should not be delayed for listing despite their low weights.\cite{30} Although BMI has been used throughout the literature to assess nutritional status, there has not been an evaluation of BMI as an indicator of morbidity and/or mortality following lung transplantation. Perhaps other
nutrition assessment tools could be used instead of BMI.

1.1.2. OTHER METHODS

SGA is a validated and reliable method of assessing nutritional status based on a patient’s nutritional history and physical examination (Appendix A). The four elements of the patient history are: weight loss, dietary intake, significant gastrointestinal symptoms, and the patient’s functional capacity. For the physical component, subcutaneous fat loss, muscle wasting, and extravascular fluid gain are examined. Combining all of these features, patients are classified as: A -- well nourished, B -- moderately malnourished, or C -- severely malnourished.

One of the most significant reports on nutritional assessment utilizing the aspects of SGA, and post surgical risk was published by Baker and colleagues. This study is most often noted as a key article of nutritional evaluation. The authors indicated that SGA, gives reproducible results with more then 80% agreement between the users (physicians, dietitians, and nurses) and is a valid measure for evaluating nutritional status before surgery.
The authors also noted that a patient's pre-operative nutritional status could predict post-operative morbidity.

Several international centers utilize SGA to determine the nutritional status of liver transplant patients. Eleven of the 13 centers contacted who responded to a questionnaire, indicated that they consistently used SGA.\textsuperscript{44} However, lung transplant patients do not have problems with ascites and edema and therefore SGA or BMI can be used in this patient population.

Studies utilizing SGA as a nutrition assessment technique have been published indicating that this technique could predict post-operative complications. A blinded prospective study of 202 patients admitted for major gastrointestinal surgery was undertaken to assess if preoperative nutritional status, as assessed by SGA, could predict post operative complications.\textsuperscript{45} The authors reported a 5% complication rate in those patients classified as A; versus a 9% complication rate in those classified as B; versus a 42% complication rate in C, the severely malnourished group. These data were statistically significant. A study indicating increased morbidity and/or mortality post OLT\textsubscript{x} was published by Pikul et al.\textsuperscript{46} The results of this study showed
that moderately to severely malnourished patients pre-transplant, using SGA, have prolonged ventilatory support and increased length of stay in the ICU. To date, there are no published lung transplant studies which utilize SGA as an indicator of nutritional status.

There are many other methods use to assess nutritional status described in the literature. Among them the Prognostic Nutrition Index (PNI), which is derived from biochemical measures such as albumin, transferrin, skin folds and immunological testing. It is reputed to determine a predicted risk of complications. However, most ESLD patients followed at the TGH had normal serum albumins. Thus the use of PNI for this patient population, may not be the best measure.

Bioelectrical Impedance (BIA) is another method used to assess a patient’s nutritional status. This method determines total body fat, body water, and lean body mass. It is a simple and rapid means of measuring body composition in normal, healthy adults. BIA has been used in extensively in the renal transplant population. However, BIA requires extra time and involves the use of expensive equipment and therefore was not
used in this present study.

Anthropometric measurements such as height, weight, and subcutaneous fat measurements using skinfold calipers are also available. These indicators have valid, published reference standards.\textsuperscript{51}

1.1.3. Choice of a Nutrition Assessment Tool

A useful marker of assessing a patient's nutritional status should be of little inconvenience to the subjects, be operated by unskilled personnel, yield highly reproducible and accurate measurements, and be relatively inexpensive. BMI meets these criteria and hence was used as the marker of nutritional status in the present study.
1.2. GENERAL SURGICAL POPULATION

1.2.1. Malnutrition

1.2.1.1. Prevalence of Malnutrition

A 50% prevalence of malnutrition was reported by Bistrian in 1977\textsuperscript{15} using anthropometric data and weight for height in 131 surgical patients surveyed. Following this, Hill reported on the nutritional status of 105 surgical patients using anthropometric data and serum albumin and found \textasciitilde 55% prevalence of malnutrition.\textsuperscript{17}

Another study reported a 3-12% prevalence of severe malnutrition in general surgical patients evidenced by a value of C using the SGA parameter.\textsuperscript{18}

Knowing that there is a \textasciitilde 50% prevalence of malnutrition in the surgical population and of this, a 12% prevalence in severely malnourished patients, it is important to acknowledge the impact this may have on morbidity and/or mortality.

1.2.1.2. Impact of Malnutrition on Morbidity and Mortality

There are several publications on malnutrition and "at risk" patients specifically related to increased morbidity and mortality.
This concept is not new. As early as 1936, Studley published results indicating that those patients who had lost 20% of their usual weight prior to surgery had a 33% mortality rate whereas those with no weight loss had a 3.5% mortality rate.\textsuperscript{19}

In 1955, Rhoads and Alexander showed that post operative infections correlated with patients pre operative nutritional status.\textsuperscript{20} As well, Hickman reported on 83 colorectal surgical patients and found that those patients who had low body weights pre-surgery had increased mortality (sensitivity = 88%).\textsuperscript{21}

1.2.1.3 Impact of Nutrition Support

A large number of surgical patients are malnourished. This malnourished state can affect morbidity and/or mortality. Now we need to address whether nutritional intervention pre-operatively will alter morbidity and/or mortality rates.

Otaki reports on 25 patients with cardiac cachexia and found an overall mortality rate of 28%.\textsuperscript{22} However, he found that those patients who had pre-operative nutrition support had a 17% mortality rate whereas, those without pre-operative nutrition support had a mortality rate of 57% (p<0.05).
The Veterans Affairs Group, undertook a study to ascertain if pre-operative nutrition intervention using TPN could decrease morbidity post-operatively.23 They found that those patients classified as severely malnourished, SGA=C, who had received TPN had fewer noninfectious complications than the controls (5 vs. 43%, p=0.03).

Fan studied 124 patients prospectively to determine if peri-operative nutritional support could improve morbidity and/or mortality post-operatively.24 The results indicated a decreased post-operative mortality rate in those patients given total parenteral nutrition (TPN) for 14 days versus control patients (34% vs. 55%, RR=0.66; 95 % CI).

Bellantone reports on a randomized controlled trial of 100 malnourished patients who underwent major surgery.25 In the treatment group consisting of malnourished and severely malnourished subjects (n=49), patients were given TPN 7 days pre-operative versus the control group (n=51) who received no treatment. The overall results indicated no difference between the two groups with respect to septic complications (30 vs 35.3%, p=NS). However, when the more malnourished patients
were further analyzed they found an increase in serious septic complications (\( p=0.09 \)) and thus recommend TPN pre-operatively to those identified malnourished patients. This appears to be in keeping with other studies. A meta-analysis completed by Detsky reviewing 18 controlled trials indicated that providing TPN for all malnourished patients may not be the most cost effective measure.\(^{18}\) However, their analysis did find that a subgroup of these patients who are considered to be severely malnourished would most likely benefit.

It appears as though nutritional support does have an impact on morbidity and/or mortality. From a cost benefit analysis, patients who are classified as severely malnourished would benefit the most.

1.2.2. Overweight/Obesity in Surgical Patients

1.2.2.1. Prevalence of overweight/obesity

The prevalence of overweight/obesity in the general population in Canada is approximately 27%. Obesity is defined as a BMI > 27kg/m\(^2\).\(^{32}\)
1.2.2.2. Impact of overweight/obesity on Morbidity and Mortality

Obese surgical patients represent a patient population with higher rates of mortality. A cross-sectional study by Mason et al report on 3,174 obese patients and found 327 patients with post-operative complications which were related to age, operative BMI and gender. However, the authors noted that post-operative mortality was low.

In their review of 10 reports examining the association between obesity and increased morbidity and/or mortality Pasulka et al found only a 3.4% mortality rate for obese patients. However there was a significant increase in post-operative complications including wound infections and wound separations.

Thomas and colleagues reported on a prospective cohort study of 2,964 >50 year old non-cardiac surgical patients. They found that overweight patients, identified as BMI >34 kg/m² had increased morbidity post-operatively with wound infections rates reported at 11% versus 4 to 7% for the non-obese patients. These patients also represented a significantly increased financial impact on the institution. Thus overweight/obese
surgical patients appear to have increased morbidity related to wound infections post surgery.

1.3. END STAGE LUNG DISEASE PATIENTS (ESLD)

1.3.1. Malnutrition

1.3.1.1. Prevalence of malnutrition in ESLD

ESLD patients are comprised of Emphysema (EMP), Chronic Obstructive Lung Disease (COPD), Primary Pulmonary Hypertension, Bronchectasis, and CF patients.

It is well documented that patients with ESLD suffer from malnutrition, referred to as lung cachexia.\(^{10-15}\) This was first described in 1955 by Dornhorst\(^{10}\) who reported that patients with Chronic Obstructive Pulmonary Disease (COPD) were thin and malnourished. Nonetheless, this issue was not addressed again until 1966 when the Veterans Administration Cooperative Study published their observation that patients with air flow obstruction were also thinner.\(^{11}\) In 1981, Hunter et al published the results of their study on the prevalence of malnutrition in COPD patients.\(^{12}\) Thirty-eight patients were randomly selected on admission to hospital. The nutritional status of these patients
was assessed using dietary intake, anthropometric data, biochemical parameters and immunological testing. They found that 50% of the COPD patients studied had anthropometric data <60% of the standard and 50% of the patients were <90% Ideal Body Weight (IBW). Driver further reinforced this point by verifying that COPD patients who developed respiratory failure were protein calorie malnourished.\(^{13}\)

In 1983, Openbrier reported on a retrospective analysis of 77 patients with Emphysema (EMP) and 30 patients with bronchitis.\(^{14}\) The nutritional status of patients with EMP and bronchitis were compared using height, weight, anthropometric and biochemical data. The results indicated that 43% of the EMP patients were <90% of their IBW versus only one bronchitis patient.

Wilson et al published a report on the relationship of weight trends and food intake in patients with EMP.\(^{15}\) During their study, they found a 46% prevalence of malnutrition.

Nightingale and authors reported a 35% prevalence of malnutrition in medical patients (including ESLD patients), using a combination of percent weight loss within the past 3 months;
BMI and Mid Arm Muscle Circumference. Patients with a BMI <19 kg/m² were classified as malnourished and patients with BMI >25 kg/m² classified as overweight. The authors stated that this 35% prevalence has essentially not changed over the past 20 years. Furthermore, they noted that completing nutrition assessments on all patients would significantly increase the workload of the dietitian. However, this would be offset by the fact that treating malnourished and “at risk” patients earlier, shorter hospital stays and fewer complications would be seen.

Overall, it appears from these studies, that ESLD patients are malnourished and the prevalence ranges from 35-50%, representing a significant number of patients. It is also interesting to note that very few studies have been done utilizing BMI.

1.3.1.2. Impact of Malnutrition on Morbidity and Mortality

Vandenburg 1967 reported that COPD patients had a 30% mortality rate 3 years after excessive weight loss and a 49% mortality rate at 5 years post weight loss.

Wilson 1989 reported on 985 malnourished COPD patients in
conjunction with 5 other participating centers. The results of this study indicated that patients who were 60-89% of Ideal Body Weight (IBW) had a 3 year mortality rate of 55%, those patients who were 90-110% IBW had a 65% mortality versus those patients who were 111-210% IBW had a mortality rate of 75%.

1.3.1.3 Impact of Malnutrition on Respiratory Mortality

There was a recent examination of nutritional status using BMI and its association with respiratory mortality in 348 ambulatory, and hospitalized subjects. The results indicated an 18% prevalence of malnutrition defined as BMI <20 kg/m² for males, and <18.8 kg/m² for females. There were 162 deaths, and those who died had a lower BMI (23.1 kg/m² vs. 24.8 kg/m², p=0.001). The authors concluded that poor nutritional status was associated with an increased risk of respiratory mortality in patients with severe COPD. However, poor nutritional status is defined as patients with BMI at <20 kg/m² and the patients in this study were within the normal limits. Thus the authors should have concluded that patients with a lower BMI were associated with an increased risk of respiratory mortality.
1.3.1.4. Impact of Nutrition Support

Nutritional support provided to both inpatients and outpatients using either increased oral intake; enteral feedings and/or TPN are reported in the literature, with varying results.

Wilson et al.\textsuperscript{56} reported on a case-control study comparing 6 malnourished stable EMP patients and 17 healthy controls. They found that, at baseline, all “cases” had below standard anthropometric data, as evidenced by lower than normal body weights and nutritional intakes. Nutritional intervention involved providing nutrition care plans with caloric intakes 150\% of subjects measured resting energy expenditures. Patients were reevaluated 3 weeks later and showed improvement in all nutrition parameters.

Efthimiou\textsuperscript{57} followed 7 malnourished COPD ambulatory patients who were supplemented with oral enteral feeds for 3 months and found an overall weight gain of 4.2 kg.

However, Lewis studied 21 ambulatory COPD patients for 8 weeks to assess the effectiveness of enteral supplementation.\textsuperscript{58} The results indicated that the supplemented patients showed no significant weight gain or changes in respiratory muscle function.
This was authors attributed to the fact that the supplemented patients decreased their oral intake. Pardy and Stauffer also found no differences in their supplemented patient population.\textsuperscript{59,60}

Goldstein reported on the effect of TPN in EMP patients and found increases in body weight, peripheral skeletal muscle function and nitrogen balance following 2 weeks of nutritional support.\textsuperscript{61}

It appears as though prospective randomized controlled studies are needed to document if the changes seen above, can alter survival.

1.3.2. \textbf{Overweight/obesity}

1.3.2.1. \textbf{Prevalence of overweight/obesity in ESLD}

While the majority of studies have been done on ESLD and malnutrition, some studies have reported a prevalence of overweight/obesity from 10-40\%, using BMI >26 kg/m\textsuperscript{2}.\textsuperscript{62}

1.3.2.2. \textbf{Impact of Obesity on Morbidity and Mortality}

There is a surprising lack of data on obesity on morbidity
and mortality in ESLD patients. The impact of nutrition support would involve weight reducing strategies for this patient population. However there are no prospective studies to indicate the changes in mortality rates with weight loss.

1.4. TRANSPLANTATION

1.4.1 Malnutrition

1.4.1.1 Prevalence of Malnutrition in Transplantation

The prevalence of malnutrition in transplantation varies within the type of organ transplanted.

1.4.1.1.1 Liver Transplant

A study involved 104 liver transplant patients were analyzed to ascertain the level of malnutrition pre-transplant. Anthropometric measurements, secretory protein levels; 24h urinary creatinine and urea nitrogen and immunological studies were the measurements used. The results of this study showed that between 68-75% of the patients were classified as malnourished.\textsuperscript{63}

Another study\textsuperscript{64} reported a 70% prevalence of malnutrition in their liver transplant population.
1.4.1.1.2. Renal Transplant

In the renal population it appears as though the prevalence of malnutrition varies from 44%\textsuperscript{65} to 55%.\textsuperscript{66}

1.4.1.1.3. Heart Transplant

Patients suffering from cardiac cachexia in the heart transplant population range from a low of 33%\textsuperscript{67} to 44.2%,\textsuperscript{68} to a high of 50%.\textsuperscript{69}

1.4.1.1.4. Lung Transplant

Since ESLD patients eventually become transplant patients, the prevalence of malnutrition in the lung transplant population would be in the range of 35-50%.\textsuperscript{10-15}

About 40% of the lung transplant patients we follow at the Toronto Hospital are malnourished as defined by a BMI <19 kg/m\textsuperscript{2}. As mentioned above, it is well known that ESLD patients are malnourished. The literature suggests that this malnourished state significantly impacts on morbidity and mortality post-operatively.

1.4.1.2. Impact of Malnutrition on Morbidity and Mortality

Studies have investigated the effects of pre-transplant
malnutrition on post-operative mortality.\textsuperscript{29,30}

\textbf{1.4.1.2.1. Lung Transplantation}

Plochl et al\textsuperscript{29} reported on ICU mortality in the lung transplant population. This retrospective chart review of 51 lung transplant patients, assessed nutritional status using BMI. Subjects, were divided into two groups: good nutritional status (patients \(>25^{th}\) percentile, equivalent to BMI >23.6 kg/m\(^2\), \(n=19\)), and patients with poor nutritional status (<\(25^{th}\) percentile, equivalent to BMI 19-23.6 kg/m\(^2\), \(n=32\)). The authors concluded that poor nutritional status, as indicated by a low BMI, was a risk factor for ICU mortality in those patients who remained in the ICU longer than 5 days. The main objective of this paper was the assessment of nutritional status as a predictor of length of stay in the ICU. This is similar to the focus of our research. However, we will also be measuring mortality at 90 days and 1 year post-transplantation length of stay in the ICU, total length of hospital stay and number of acute rejection episodes, as this has never been documented in the literature.

Snell et al,\textsuperscript{30} retrospectively analyzed the effect of BMI on pre transplant and post transplant survival in 45 CF lung
transplant patients. They found that a low BMI at the time of listing was a significant predictor of death on the waiting list (RR=4.6). Furthermore they found that a combination of a BMI <18 kg/m² and being female resulted in a 21% 1 year survival rate on the waiting list. Of the 45 CF patients transplanted, 5 died within 90 days and 10 patients died >90 days post-transplant. The authors concluded that patients with BMI <18 kg/m² should be regarded as being at significant risk of not surviving until transplant and that their listing should not be delayed to improve their weight. The purpose of Snell’s study was to avoid waiting to list CF patients for transplantation. However, Snell did not discuss the impact of increased severity of illness on survival post lung transplant in the CF population: Such information has not been documented in the literature.

1.4.1.2.2. Heart and Lung Transplantation

Sharples reports on 13 CF patients who received a heart and lung transplant. The results of this study indicated that of the eight patients that died post-operatively, 87% were below the median percent predicted weight for height. (RR=0.96; CI, 0.92 to 0.99) The authors noted that
poorly nourished CF patients succumbed to post-operative complications as opposed to dying while waiting for transplant. However, since several CF patients have impaired growth, the nutritional measure used in this study may not have been the most appropriate. Therefore, the authors concluded there was only slight evidence of pre-transplant nutritional status influencing post-transplant morbidity.

1.4.1.2.3. Intestinal Transplantation

Rovera \(^7\) reports on 22 patients who received intestinal transplants. They report that all recipients were well nourished pre-transplant (BMI = 23±1.0) and all patients remained alive with functioning grafts one year post-transplantation. It should be noted these patients were on TPN pre- and post-transplant and would therefore be better nourished.

1.4.1.2.4. Liver Transplantation

Selberg et al\(^7\) reported on a prospective cohort study of 150 patients with end stage liver disease. All patients were randomized into either the study group or validation group with 75 patients in each category. These patients were then followed prospectively for 46±16 months after orthotopic liver
transplantation ($\text{OLT}_x$). The results of this study found that patients identified pre-$\text{OLT}_x$ with poor nutritional status, measured by BIA, anthropometry, and resting energy expenditure, had decreased 1 and 5 year survival rates.

1.4.1.3. Impact of Nutrition Support

To date, there are no data on the impact of pre-operative nutrition support following lung transplantation.

Reilly$^{73}$ reports on a randomized prospective study involving 28 post-operative liver transplant patients. Ten patients received no TPN; 8 patients received the standard TPN hospital solution and 10 patients received TPN supplemented with branched chain amino acids. Their results indicated that the two groups receiving TPN had better nitrogen balance ($p<.001$) and had a shorter length of stay in the ICU (LOS (ICU)), although not statistically significant.

More importantly, as one author discusses,$^{74}$ the timing of the nutritional intervention is a significant factor to be considered when providing nutrition support.
1.4.2. OVERWEIGHT/OBESITY

1.4.2.1. Prevalence of Overweight/obesity in Transplantation

Approximately 20% of the patients seen at the lung transplant program of the TGH are overweight/obese as defined by a BMI >27kg/m². This is similar to what is reported in the renal transplant literature. There have been no reports published on obesity in the lung transplant population.

1.4.2.2. Impact of overweight/obesity on Morbidity and Mortality

The effect of obesity on morbidity and mortality post transplant has been reported in a variety of transplant patients with differing results.

1.4.2.2.1. Liver Transplantation

A review of 40 morbidly obese liver transplant patients (BMI >30 kg/m²) and 61 time matched controls, found that survival at 1 year following transplantation was similar for obese and non-obese patients.

However, a study by Keefe examined the impact of pre-transplant obesity on post-operative morbidity and/or mortality in 18 OLTx patients using BMI >33 kg/m². The results of this study
showed no differences in morbidity and/or mortality in the obese group versus the non-obese patients.

1.4.2.2.2. Pancreas and Renal Transplantation

In a series of patients, Bumgardner\textsuperscript{78} found that actuarial graft survival for both pancreas and renal recipients were significantly decreased in patients with BMI >27 kg/m\textsuperscript{2}.

1.4.2.2.3. Renal Transplantation

It appears as though the majority of pre-transplant obesity research has been done in the renal transplant population with varying conclusions.

Halme et al\textsuperscript{79} reported decreased survival rates in obese post renal transplant patients. They reported one year survival rates of 68\% for obese patients versus 84\% for non-obese. Based on this, these authors will not accept patients with a BMI >30 kg/m\textsuperscript{2}.

Gill et al\textsuperscript{80} report on an increased loss of 1 year graft survival and increased complications in obese renal versus non-obese renal patients. In agreement with this, Holley\textsuperscript{81} found increased deaths and increased complications following renal transplantation in obese patients. As well, Blumke\textsuperscript{82} reported on
obese renal transplant patients, defined as >120% above the normal weight. The results of this study found a statistically significant (p=<.0003) lower 4 year graft survival rate (58.2%) in obese patients versus non-obese (84.2%). Drafts et al 63 evaluated pre-transplant obesity on post-transplant complications using BMI. Draft's group did not use the current standards of defining obesity as defined by Health and Welfare Canada.6 Non-obese patients, 81% of the total population, were classified as Group 1 (BMI <30 kg/m²); moderately obese, 17% of the total population, as Group 2 (BMI >30 to 40 kg/m²); and morbidly obese, 2% of the population, as Group 3 (BMI >40 kg/m²). They found increased wound infections in Groups 2 and 3 versus Group 1 (2.9% and 14.3% vs .6%, respectively, P=0.002). They also reported an increased delayed graft function in Groups 2 and 3 versus Group 1, but this was not statistically significant.

Pirsch et al 84 reported on 118 obese renal transplant patients using BMI as a marker of nutritional status. Mild obesity was defined as BMI > 27.5 kg/m², and obesity as BMI >30 kg/m². The results of this report indicated that obese patients had a significantly increased incidence of delayed graft function with an
increased risk of wound and urologic complications.

In contrast to this, Merion et al\textsuperscript{85} reported on 40 obese renal transplant patients. The purpose of this study was to ascertain if pre-transplant obesity, defined as 120\% above ideal body weight, influenced post-operative mortality and/or morbidity. Their results indicated that obese patients had a 17.5\% rate of wound infections versus 6.3\% for non-obese (P=0.036) but no other incidence of complications or mortality. They concluded that obesity should not be a contraindication to renal transplantation.

1.4.2.3. Impact of Nutrition on Morbidity and Mortality

There have been no studies completed on the deleterious or beneficial effect of weight reducing pre surgery, and its effect on outcome post surgery. It would be beneficial to design an interventional study examining the effect of weight loss on post operative morbidity and mortality.

1.5. RISK FACTORS AFFECTING MORTALITY

The following variables could influence mortality and therefore could affect the interpretation of study results. These
are age, gender, type of disease and CMV mismatch. Thus, these variable must be controlled for in the final analyses. Patients who are older, approximately over 65 years of age, tend to do worse than the younger lung transplant patients. A univariate analysis of early mortality in the lung transplant population identified that male gender was an early significant risk factor for mortality. CF patients are at increased risk of developing bacterial pneumonia, resulting in increased rates or mortality. Furthermore, CF cepacia positive patients have increased mortality post-transplantation. Cytomegalovirus (CMV) mismatch represents an increased risk of early mortality in the lung transplant population as compared with liver, heart or renal transplant.

1.6. SUMMARY OF THE LITERATURE REVIEW

In summary, there appears to be evidence in the literature that there is an association between malnourished and/or obese pre-transplant patients and increased mortality post-transplantation. However, there are only a few studies using BMI pre-transplant as a predictor of mortality and morbidity post-
transplant. As well, the majority of the research has been done in the renal transplant population and little has been done in the lung transplant patients. Currently only two studies were published in the lung transplant literature utilizing BMI. Further research is now needed to help establish an association between pre-transplant nutritional status and post-operative morbidity and mortality using BMI specifically in the lung transplant population. This research is important to identify patients with the best long-term survival to optimize organ utilization. The results may help determine the timing of transplantation assessment based on BMI and identify patient who may benefit from nutritional intervention.
1.7. HYPOTHESIS AND OBJECTIVES

The primary hypothesis of this study was that pre-transplant BMI is a predictor of morbidity and mortality in ESLD patients post-transplantation.

The objectives were to determine if patients with a pre-transplant BMI <20 kg/m² and >25 kg/m² have increased 90 day and 1 year mortality, increased length of stay in the ICU, increased length of hospital stay, and increased number of rejection episodes, following lung transplantation.
CHAPTER 2. MATERIALS AND METHODS

2.1. SUBJECTS

Two hundred and forty patients from November 1983 (program inception) to April 1997 received either single lung transplants (SLT) or bilateral lung transplants (BLT).

At the time of assessment, the patients were stable, ambulatory and met the following criteria: patients who have end-stage disease; off or on low doses of prednisone; life expectancy of 6 months; absence of severe hepatic, renal or cardiac disease; ability to adhere to a complex medical program; adequate rehabilitation potential and HIV negative.

2.2. STUDY DESIGN

The study design was a retrospective chart review of the lung transplant program patients. As part of the pre-transplant protocol, all patients underwent a thorough nutritional assessment, which was recorded in the dietitians charts. The mortality data were also collected from the dietitian's charts, while the morbidity data were from hospital charts. The nutritional assessment performed by the dietitian included: BMI,
age, gender, disease category. For the purposes of this study, BMI was calculated at the time of the assessment. If the patient was transplanted within six to eight months of the assessment, the BMI at initial assessment was used. If the patient was transplanted after that time, the BMI was recorded at or as close to transplant as possible. As defined in the literature, a normal BMI for this study was established to be between 20-25 kg/m² with an odds ratio (OR) equal to 1.0. Other BMI categories were chosen to identify the overweight (25 to 27 kg/m²), obese (>27 kg/m²), and underweight (<20 kg/m²). From clinical practice, the decision was made to divide the underweight category into two groups since those patients with a BMI <17 kg/m² appeared to have a higher mortality rate. Therefore, the underweight BMI categories were chosen as <17 kg/m² and 17 to <20 kg/m².

As appropriate, CMV status, transplant type, the cause of death, LOS (ICU), and LOS (H) were retrieved from hospital charts. Dependent measures included mortality within the first 90 days and 1 year post transplantation. Morbidity was examined by evaluating LOS (ICU), LOS (H), and the number of patients who had rejection episodes within the first 90 days.
Rejection episodes were documented as boluses of solumedrol (a drug to treat rejection). In order to confirm the actual LOS (ICU), several areas of the medical notes were compared. There can be up to a 24-hour discrepancy from the time a physician writes a discharge note to when the patient actually leaves the ICU. Thus physicians' discharge notes were compared with the transplant nursing staff notes. The charted discharge from hospital date was verified with dates on prescriptions written and nursing staff discharge notes.

2.3. STATISTICAL ANALYSES

Logistic Regression was used for uni- and multi-variate analysis of the primary outcome measure of 90 day mortality. Measures were adjusted for the following risk factors: recipient age and gender, disease category, pre-transplant CMV serology; and donor age and gender, and CMV serology. All tests were two-tailed, statistical significance was considered when P<0.05.

Life table analyses were completed for the secondary outcome measures of LOS (ICU), LOS (H) and survival at one
year. Survival estimates were obtained using Kaplan Meier curves and these were compared using the Wilcoxon test. If the results of these analysis indicated that at least two of the distributions were significantly different from each other, then a comparison of each BMI category with the reference BMI category (20-25 kg/m²) was completed.

Power analysis was evaluated using the Distribution Function and Probability Calculator Version 2.3.
CHAPTER 3. RESULTS

3.1. SUBJECTS

A retrospective review of 240 patients from the lung transplant program at the TGH, yielded a total of 251 lung transplants. Eleven patients were re-transplanted and thus there were 251 transplants in 240 patients. An additional eleven patients did not have complete data available. Thus mortality data for this study are based on 229 patients. There were 104 female and 125 male recipients. Ages, represented as means±SD, were 42.1±12.8 and 43.6±13.2 for female and males recipients, respectively. Donors ages were 38.0±12.8 and 30.8±11.9 for female and males, respectively. Hospital charts were not available for 24 patients; thus, morbidity data are based on 203 patients.

3.2. PRIMARY OUTCOME MEASURE

BMI and mortality at 90 days indicated that patients with BMI <17 kg/m² tended to have an increased risk of dying (p=0.085, Table 3.1). The results of the power analysis indicated that the power to detect a statistically significant differences was lacking.
To achieve statistical significance, 250-300 patients would be needed to achieve 80% power with alpha of .05. Patients within the BMI group 17 to <20 kg/m² (n=62) had a risk of dying not significantly different from the reference category. Results of the power analysis for this group indicated the sufficient power was not lacking. Patients with BMI >25 to 27 kg/m² the OR for mortality equals 3.6 (p=0.069). The risk of dying for these patients was four times greater than the reference group. Power analysis for this group indicated that 250-300 patients would be needed to detect a statistically significant result. For the patients with BMI >27 kg/m², the risk of dying within 90 days post-transplantation was significantly increased (OR=5.0, p=0.003).

3.3. SECONDARY OUTCOME MEASURES

Mortality, BMI, and disease states at one year are shown in Table 3.2. BMI had no effect on one year survival. There were 53 deaths within one year post-transplantation. The major causes of late deaths were sepsis and Bronchiolitis Obliterans
(BO). The one year survival rate was 75%. The survival of patients at one year by BMI category can be seen in Figure 3.1.

The results of the Kaplan Meier analysis of BMI and LOS (ICU), indicated that at least two of the distributions were significantly different (p=0.0142, Table 3.3). A comparison of each BMI category with the reference category was completed.

The median LOS (ICU) for the adequately nourished BMI group of 20 to 25 kg/m² (n=74), was 5 days, with the first and third interquartiles of 3 to 9 days. For those patients with BMI <17 kg/m² (n=18), median LOS (ICU) = 6 days, with the first and third interquartiles of 2 to 19 days, p=0.819. Patients in the BMI category of 17 to <20 kg/m²; (n=57), LOS (ICU)= 7 days, with the first and third interquartiles of 4 to 17 days, p=0.0626. Patients in the BMI >25 and <27 kg/m² group (n=19), LOS (ICU)=13 days, with first and third interquartiles of 5 to 20 days, p=0.0122. For those patients in the group BMI >27 kg/m² (n=37), LOS (ICU)=11 days with first and third interquartiles of 4 to 32 days, p=0.0063. The percentage of patients remaining in the ICU by BMI category can be seen in Figure 3.2.
The results of the analysis for LOS (H) with BMI indicated there was no difference between the groups (p=0.1460, Table 3.4). Thus, a comparison of each BMI category with the reference category was not indicated.

The average LOS(H) for adequately nourished patients was 25 days \( (n=74) \) with first and third interquartiles of 19 to 41 days, 20% of the time was spent in the ICU. For those patients with BMI \(<17 \text{ kg/m}^2 (n=18)\), average LOS (H) was 32 days, with the first and third interquartiles of 19 to 51 days, 18.7% of the time was spent in the ICU. For those patients with BMI 17 to \(<20 \text{ kg/m}^2 (n=57)\), average LOS (H) was 33 days with the first and third interquartiles of 23 to 52 days, 21.2% of the time was spent in the ICU. For those patients with BMI 25 to 27 \text{ kg/m}^2, average LOS(H) was 32 days, with the first and third interquartiles of 25 to 45, 40.6% of the time was in the ICU. For those patients with BMI \(>27 \text{ kg/m}^2\), average LOS(H) was 34 days, with first and third interquartiles of 24 to 66 days, 32.3% of that time was spent in the ICU. The percentage of patients remaining in the hospital by BMI category can be seen in Figure 3.3.
The results of the analysis of the 205 patients examined for episodes of rejection indicated that 162/205 (79%) had no episodes of rejections (Table 3.5). Twenty six of the 205 patients (13%) had one episode of rejection and 17/205 (8%) had 2 episodes of rejection from 0 to 90 days post-transplantation. This was an observation only, and these results are not statistically significant.
Table 3.1. Likelihood estimates of the risk of death within 90 days of lung transplantation by BMI category.

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>n_d / n*</th>
<th>COEFFICIENT</th>
<th>ODDS RATIO 95% CI**</th>
<th>p VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;17</td>
<td>4 / 23</td>
<td>1.2130</td>
<td>3.7</td>
<td>0.9 - 13.4</td>
</tr>
<tr>
<td>17 to &lt;20</td>
<td>6 / 62</td>
<td>0.4372</td>
<td>1.6</td>
<td>0.5 - 5.0</td>
</tr>
<tr>
<td>20 to 25</td>
<td>7 / 82</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25 to 27</td>
<td>4 / 19</td>
<td>1.2864</td>
<td>3.6</td>
<td>0.9 - 14.5</td>
</tr>
<tr>
<td>&gt;27</td>
<td>11/ 43</td>
<td>1.6066</td>
<td>5.0</td>
<td>1.4 - 14.6</td>
</tr>
</tbody>
</table>

Recipient

Gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>n_d / n*</th>
<th>COEFFICIENT</th>
<th>ODDS RATIO 95% CI**</th>
<th>p VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24/125</td>
<td>1.2866</td>
<td>3.6</td>
<td>1.5 - 8.8</td>
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<tr>
<td>Female</td>
<td>8/104</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* n_d / n = Number of deaths / number of recipients per BMI category
** 95% Confidence interval (lower limit - upper limit)
Odds Ratio is by multi-variate analysis.
### Table 3.2. Mortality and BMI (kg/m²) at one year post lung transplantation.

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>&lt;17</th>
<th>17 to&lt;20</th>
<th>20 to 25</th>
<th>&gt;25 to 27</th>
<th>&gt;27</th>
<th>TOTAL</th>
</tr>
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<tbody>
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<td>1</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>12</td>
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<tr>
<td>EMP</td>
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<td>2</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>CF</td>
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<td>6</td>
<td>0</td>
<td>1</td>
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<td>PPH</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>EMP A1AD</td>
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<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>8</td>
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<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
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<tr>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>1</td>
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<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>P.Veno.</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>11</td>
<td>16</td>
<td>8</td>
<td>11</td>
<td>53</td>
</tr>
</tbody>
</table>


Results are not statistically significant.
Figure 3.1. Survival of patients at one year post lung transplantation by BMI category.
Table 3.3. Post lung transplant length of stay in intensive care unit, by BMI category.

<table>
<thead>
<tr>
<th>BMI (kg/m²) (n=205)</th>
<th>MEDIAN (Days)</th>
<th>Q₁ - Q₃ (Days)</th>
<th>p VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;17 (n=18)</td>
<td>6</td>
<td>2-19</td>
<td>0.8197</td>
</tr>
<tr>
<td>17 to &lt;20 (n=57)</td>
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<td>4-17</td>
<td>0.0626</td>
</tr>
<tr>
<td>20 to 25 (n=74)</td>
<td>5</td>
<td>3-9</td>
<td></td>
</tr>
<tr>
<td>&gt;25 to 27 (n=19)</td>
<td>13</td>
<td>5-20</td>
<td>0.0122</td>
</tr>
<tr>
<td>&gt;27 (n=37)</td>
<td>11</td>
<td>4-32</td>
<td>0.0063</td>
</tr>
</tbody>
</table>
Figure 3.2. Percentage of patients remaining in ICU post lung transplantation by BMI category.
Table 3.4. Total length of stay in the hospital post lung transplantation, by BMI category.

<table>
<thead>
<tr>
<th>BMI (kg/m²) (n=205)</th>
<th>MEDIAN (days)</th>
<th>Q₁- Q₃ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;17 (n=18)</td>
<td>32</td>
<td>19-51</td>
</tr>
<tr>
<td>17 to &lt;20 (n=57)</td>
<td>33</td>
<td>23-52</td>
</tr>
<tr>
<td>20 to 25 (n=74)</td>
<td>25</td>
<td>19-41</td>
</tr>
<tr>
<td>&gt;25 to 27 (n=19)</td>
<td>32</td>
<td>25-45</td>
</tr>
<tr>
<td>&gt;27 (n=37)</td>
<td>34</td>
<td>24-66</td>
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</tbody>
</table>

Wilcoxon analysis p=0.1460
Figure 3.3. Percentage of patients remaining in hospital post lung transplantation by BMI category.
Table 3.5. Percentage of patients who presented with acute rejection episodes within 90 days post lung transplantation, by BMI category.*

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>REJECTION % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;17 (n=18)</td>
<td>11.1 (2)</td>
</tr>
<tr>
<td>17 to &lt;20 (n=57)</td>
<td>24.6 (14)</td>
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<td>20 to 25 (n=74)</td>
<td>18.9 (14)</td>
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<tr>
<td>&gt;25 to 27 (n=19)</td>
<td>31.6 (6)</td>
</tr>
<tr>
<td>&gt;27 (n=37)</td>
<td>18.9 (7)</td>
</tr>
</tbody>
</table>

*Observational data.
Distribution of CMV serology results are shown in Table 3.6. Frequencies were similar across groups and gender. As seen in Table 3.7, cystic fibrosis was the most common indication for transplant (24%), followed by emphysema, (18%).

Thirty two deaths occurred within 90 days post lung transplantation, 24 males and 8 females. Causes of death by BMI and gender appear in Table 3.8. The major causes of death for males were infections; whereas for females, infectious related deaths occurred <50% of the time. In males and females with a BMI of <25 kg/m², infectious deaths equaled 13 compared to 6 in patients with BMI of ≥25 kg/m².

Table 3.9 shows possible risk factors associated with post lung transplant mortality. In the BMI group <17 kg/m², there were 9 CF patients. Of these, 5 were Cepacia positive. Three of the five Cepacia positive patients died (60%). There were 4 Cepacia negative patients in this group and none of them died. Twenty-five CF patients were in the 17 to <20 kg/m². Fifteen patients were Cepacia positive. Four Cepacia positive patients died (~30%). Of the 10 Cepacia negative patients, one died. There were 18 CF patients in the reference group (20-25 kg/m²),
six were Cepacia positive and none of these patients died. There was one CF Cepacia positive patient in the BMI >27 kg/m² group and none in either the 20 to 25 or the >25 to 27 kg/m² categories. There was one CF diabetic patient in each of the BMI categories <17 and 17 to <20 kg/m². There were no diabetic patients in the 20 to 25 or the >25 to 27 kg/m² categories. The >27 kg/m² category included one diabetic patient. High blood pressure and dyslipidemia were present in the >27 kg/m² category but not in the other BMI groups (Table 3.9).

Results of uni-variate analyses are shown in Table 3.10. Estimated OR for death within 90 days of lung transplant shows a J curve for BMI and significance was seen only for the >27 kg/m² category. Donor male gender as well as recipient male gender showed increased OR for early death, but only recipient gender was statistically significant p=0.011. Recipients of bilateral lung grafts also appeared to have an increased risk of early death, but this was not statistically significant. The model obtained on multi-variate analysis, included only BMI and recipient gender as predictors of early mortality. Though the OR for type of transplant remained unchanged, the P-value for type of
transplant increased to 0.2015 when BMI and recipient's gender were included in the model.
Table 3.6. CMV serology pre-transplant status.

<table>
<thead>
<tr>
<th>RECIPIENT / DONOR</th>
<th>- / -</th>
<th>- / +</th>
<th>+ / -</th>
<th>+ / +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>22</td>
<td>24</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>(%)</td>
<td>(21)</td>
<td>(23)</td>
<td>(28)</td>
<td>(28)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>28</td>
<td>38</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>(%)</td>
<td>(27)</td>
<td>(37)</td>
<td>(30)</td>
<td>(26)</td>
</tr>
</tbody>
</table>

1 missing (male)
Table 3.7. Main indications for lung transplantation, as total number and percentage of patient population.

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis</td>
<td>55</td>
<td>24.0</td>
</tr>
<tr>
<td>Emphysema</td>
<td>41</td>
<td>18.0</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>39</td>
<td>17.0</td>
</tr>
<tr>
<td>Empysema-Alpha1 ATD</td>
<td>34</td>
<td>14.8</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>16</td>
<td>7.0</td>
</tr>
<tr>
<td>Eisenmenger's</td>
<td>8</td>
<td>3.5</td>
</tr>
<tr>
<td>Bronchiolitis Obliterans</td>
<td>6</td>
<td>3.1</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>7</td>
<td>2.6</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>6</td>
<td>2.6</td>
</tr>
<tr>
<td>Eosinophilic Granuloma</td>
<td>5</td>
<td>2.2</td>
</tr>
<tr>
<td>COPD</td>
<td>4</td>
<td>1.7</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>3.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>CAUSES</th>
<th>MORTALITY FEMALE (n=8)</th>
<th>MORTALITY MALE (n=24)</th>
<th>TOTAL # OF PATIENTS n (F:M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;17</td>
<td>Sepsis</td>
<td>2</td>
<td>2</td>
<td>23 (14:9)</td>
</tr>
<tr>
<td>17 to &lt;20</td>
<td>Sepsis</td>
<td>1</td>
<td>2</td>
<td>62 (35:27)</td>
</tr>
<tr>
<td></td>
<td>CMV</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsA Toxicity</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>20 to 25</td>
<td>Sepsis</td>
<td>0</td>
<td>5</td>
<td>82 (24:58)</td>
</tr>
<tr>
<td></td>
<td>CMV Tracheal Dehiscence</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intra-operative Hemorrhage.</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;25 to 27</td>
<td>Sepsis</td>
<td>0</td>
<td>2</td>
<td>19 (9:10)</td>
</tr>
<tr>
<td></td>
<td>Airway</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Necrosis</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSOF</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;27</td>
<td>Sepsis</td>
<td>0</td>
<td>4</td>
<td>43 (22:21)</td>
</tr>
<tr>
<td></td>
<td>CVA</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tracheal. Dehiscence</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Air Emboli</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSOF</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

CMV Pneumonia=cytomegalovirus pneumonia. CsA=cyclosporin. MSOF=multi-system organ failure. CVA=cerebral vascular accident.
Table 3.9. Causes of death and risk factors associated with post lung transplant mortality by BMI category.

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>CAUSES OF DEATH</th>
<th>PRE-TX DIAGNOSES</th>
<th>ADDITIONAL RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;17</td>
<td>Sepsis (n=4)</td>
<td>CFC⁺ (n=3)</td>
<td>CF Diabetic (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMPA1AD (n=1)</td>
<td></td>
</tr>
<tr>
<td>17 to &lt;20</td>
<td>Sepsis (n=6)</td>
<td>CFC⁺ (n=5)</td>
<td>CF Diabetic (n=1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF (n=1)</td>
<td></td>
</tr>
<tr>
<td>20 to 25</td>
<td>Sepsis</td>
<td>EMPA1AD (n=2)</td>
<td>No Diabetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMP (n=1)</td>
<td>No HBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPH (n=1)</td>
<td>No High Chol</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage (n=7)</td>
<td>PF (n=1)</td>
<td>Other (n=2)</td>
</tr>
<tr>
<td>&gt;25 to 27</td>
<td>Sepsis</td>
<td>CFC⁺ (n=1)</td>
<td>No Diabetics</td>
</tr>
<tr>
<td></td>
<td>Airway Necrosis (n=4)</td>
<td>PF (n=1)</td>
<td>No HBP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EMPA1AD (n=1)</td>
<td>Other (n=1)</td>
</tr>
<tr>
<td>&gt;27</td>
<td>Sepsis</td>
<td>PF (n=4)</td>
<td>Diabetic (n=1)</td>
</tr>
<tr>
<td></td>
<td>Tracheal dehiscence (n=11)</td>
<td>PPH (n=2)</td>
<td>HBP (n=1)</td>
</tr>
<tr>
<td></td>
<td>Air emboli</td>
<td>EMPA1AD (n=2)</td>
<td>Chol (n=2)</td>
</tr>
<tr>
<td></td>
<td>(n=11)</td>
<td>CFC⁺ (n=1)</td>
<td>Prednisone (n=2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other (n=2)</td>
<td></td>
</tr>
</tbody>
</table>

Pre-tx=pre-transplant. CMV trach dehiscence=cytomegalovirus tracheal dehiscence. CFC⁺=Cystic Fibrosis, Burkholderia cepacia positive. EMPA1AD=emphysema alpha 1 anti-trypsin deficiency. PF=Pulmonary Fibrosis. CF=Cystic Fibrosis. PPH=primary pulmonary hypertension. HBP=high blood pressure. High Chol=high cholesterol.
Table 3.10. Results of uni-variate analysis of risk factors and mortality.

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>P VALUE</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient Age</td>
<td>0.200</td>
<td>1.0</td>
</tr>
<tr>
<td>Donor Age</td>
<td>0.638</td>
<td>1.0</td>
</tr>
<tr>
<td>BMI 20 to 25*</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;17</td>
<td>0.230</td>
<td>2.3</td>
</tr>
<tr>
<td>17 to &lt;20</td>
<td>0.813</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;25 to 27</td>
<td>0.127</td>
<td>2.9</td>
</tr>
<tr>
<td>&gt;27</td>
<td>0.006</td>
<td>4.2</td>
</tr>
<tr>
<td>Recipient Gender (Male)</td>
<td>0.011</td>
<td>3.0</td>
</tr>
<tr>
<td>Donor Gender (Male)</td>
<td>0.285</td>
<td>1.5</td>
</tr>
<tr>
<td>Recipient CMV Serology (+)</td>
<td>0.784</td>
<td>1.1</td>
</tr>
<tr>
<td>Donor CMV Serology (+)</td>
<td>0.867</td>
<td>1.1</td>
</tr>
<tr>
<td>Transplant Type (Bilateral)</td>
<td>0.146</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Emphysema</td>
<td>0.048</td>
<td>0.1</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>0.977</td>
<td>1.0</td>
</tr>
<tr>
<td>Primary Pulmonary Hypertension</td>
<td>0.944</td>
<td>1.0</td>
</tr>
<tr>
<td>Emphysema alpha 1 anti-trypsin</td>
<td>0.973</td>
<td>1.0</td>
</tr>
<tr>
<td>deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.591</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Logistic Regression was used for the analysis.

*BMI 20 to 25=reference category.
CHAPTER 4. DISCUSSION AND LIMITATIONS

4.1. DISCUSSION

The purpose of this study was to determine if patients with BMI $<20 \text{ kg/m}^2$ and $>25 \text{ kg/m}^2$ pre-transplant had increased 90 day and 1 year mortality, increased LOS (ICU), increased LOS (H), and increased number of rejection episodes, following lung transplantation.

The lung transplant population was chosen since very little data has been published in the area of BMI as a prognostic factor for mortality; increased LOS (ICU) and LOS(H). BMI was selected as the primary index for the following reasons. BMI is a simple and inexpensive procedure, BMI captures both malnourished and overweight/obese patients, and there is a relationship established, in the literature, between BMI and morbidity and mortality in the general population. However, BMI literature in the transplant population is sparse, with the majority of the studies in the renal transplant population. To date, there are no studies using BMI as a prognostic factor with 90 day mortality within the lung transplant population.
This study appears to support the hypothesis that BMI is a prognostic factor for 90 day mortality, increased LOS (ICU) and LOS(H) in the lung transplant population. This is an important issue because with an increasing number of potential candidates for lung transplantation, and an increasing organ donor shortage, it becomes imperative to be able to identify patients with the best long term survival.

Survival rate at 90 days in this population was 86%. Other lung transplant centers, Smith report 89% and Norgard 85% survival rate. The major cause of deaths in this study were infections. Reports of infectious complications being the major cause of death in other studies on lung transplantation has been reported previously, at TGH.95 Others also report that infections remain a common problem after lung transplantation despite recent antibiotic coverage. The likely reason that the majority of patients who die early from infections, may be due to the fact that the lung is continuously exposed to the environment.97 Furthermore, the literature supports that patients with low body weights pre-surgery have increased morbidity and mortality post surgery, due to infectious complications.19-21
Sepsis was the major cause of death in patients with BMI<25 kg/m². Other causes of death in this <25 kg/m² BMI group were CMV pneumonia, pneumonia, CMV tracheal dehiscence and intra-operative hemorrhage. (Table 3.8). For those patients in the >25 kg/m² group, sepsis occurred less often then in the <25 kg/m². Other causes of death for this group were wound dehiscence, air embolism, MSOF, cardiovascular and CVA. There may be other reasons for the increased mortality seen in this patient population (Table 3.9). It appears that patients with a low BMI may have increased mortality due to the fact they were Cepacia positive. Burkholderia Cepacia is a multi-resistant bacteria and over one half of CF patients are colonized with this bacteria. It is known from the literature that Cepacia positive patients die more frequently post transplantation than Cepacia negative patients. It should be noted that if Cepacia accounted for the increased mortality, then the same proportion of Cepacia positive patients would die in the other BMI categories. Data from this study does not support this. However, it could be postulated that those patients who were Cepacia positive and more adequately nourished (BMI 20 to 25
kg/m²) were better able to fight infections, thus, leading to decreased mortality. It may be a combination of a low BMI and Cepacia positive that results in the patients increased mortality. As well, a diagnosis of CF, may cause the increased mortality.²⁸

For the overweight patients it doesn't appear as though the other possible risk factors, such as diabetes, high blood pressure or dyslipidemia,⁸ played a role in the increased mortality (Table 3.9). However, overweight and obese patients undergoing surgery have increased rates of mortality, due to surgical difficulties.⁹⁸⁻¹⁰⁰ These surgical complications include wound dehiscence,⁹⁸ air embolisms,⁹⁹ and MSOF.¹⁰⁰ Overweight/obese patients represented an increased median length of stay in the hospital, although not statistically significant. These results appear to be in keeping with what was found in the literature. Choban¹⁰¹ reported increased number and incidence of nosocomial infections in obese and severely obese patients, using BMI as their marker, compared to the adequately nourished group. As well, Forse,¹⁰² reported on a 2.8% wound infection rate for adequately nourished surgical patients (BMI=22±4 kg/m²) versus an 8% wound infection rate for morbidly obese surgical
patients (BMI=46±6 kg/m²). In this study, patients with BMI >27 kg/m² were associated with a significant increased risk of mortality. Nutritional intervention strategies for weight loss for these patients have been implemented. A thorough discussion of research results is given to all overweight/obese patients during the assessment phase with the goal of weight loss. Most patients wait 1-2 years before receiving their transplant, allowing ample opportunity to teach, encourage and support these patients through their weight loss program. While the data from this study support that patients with BMI >27 kg/m² have increased mortality and morbidity, the Toronto General Hospital lung transplant program, has not yet made a decision to exclude these patients from acceptance. The program has chosen to accept these patients with the goal of losing weight prior to the transplant. This decision is consistent with other authors regarding accepting overweight/obese patients. As discussed earlier, Drafts⁸³ agrees that patients should receive aggressive pre-transplant nutrition counseling and should not be excluded for transplantation. In contrast, there are however other programs that will not accept overweight/obese patients for
transplantation due to the increased mortality. Currently there are no studies assessing the impact of pre-transplant weight loss on morbidity and mortality post transplantation. A future prospective randomized study to assess this impact could be easily achieved in this patient population. A study of this nature would involve randomizing patients with pre-transplant BMI >27 kg/m² to receive either nutritional intervention (weight loss) or no intervention and following them post transplantation to assess the impact on mortality and morbidity. This type of research would add significantly to the knowledge in this area.

The number of rejection episodes based on BMI categories indicated that 162/205 (79%) of the patients had no episodes of acute rejection within the first 90 days. This was an observation only and no statistical analyses were performed on the data. The most striking result was that those patients with BMI <17 kg/m² had the lowest rates of rejection. This could be expected as these patients would most likely represent the most malnourished and therefore the most immunosuppressed. Protein energy malnutrition and micronutrient deficiencies have been reported to cause immune dysfunction, especially cellular
immunity.\textsuperscript{103} This immune dysfunction may reduce the number of rejection episodes.\textsuperscript{103} Furthermore, Field discusses that nutritional states can impact the immune system and as well, altered immune status can impact on nutritional status.\textsuperscript{104} For the remainder of the patients in the BMI categories more episodes of rejection were seen. It could be postulated that these well nourished patients may have had better immune systems and would therefore be able to mount the greatest immune response. There are no studies in the lung transplant population on overweight and/or obesity following lung transplantation. The literature suggests that with increasing weight there is increasing risk of developing diabetes which could negatively alter the immune state.\textsuperscript{105} However, from the present study, increased incidence of diabetes was not seen. While this is an interesting finding it is as yet, unexplained.

BMI had no effect on survival at one year, but this was to be expected since pre-transplant BMI would most likely have the greatest effect within 30-90 days post transplantation. From clinical observation, it appears that the pre-transplant BMI is the same or close to the BMI value 30-90 days post transplantation;
however, by one year the BMI is different from the pre-transplant BMI. By one year, other variables would be involved; such as, chronic rejection\textsuperscript{107} and therefore BMI would play much less of a role at that time. Based on these data the current survival rate at one year is 77%. This is similar to what was reported (69%) by the International Society for Heart and Lung Transplantation registry.\textsuperscript{106} In this study there were 21 late deaths and the causes were Bronchiloitias Obliterans Syndrome (BOS) and sepsis. Cooper found a similar rate of late deaths (13).\textsuperscript{90} The most common cause of late deaths as discussed in the literature, has been linked to BOS.\textsuperscript{107}

Another factor to consider is the additional costs associated with increased LOS (ICU) and LOS (H). For the patients with BMI <17 kg/m\textsuperscript{2}, a 6 day stay in the ICU versus the reference category of 5 days, would represent an additional cost of $1500 per patient, based on the current TGH figure of $1500/day for an ICU bed. Eighteen patients fell into this category, which translates to an additional cost of $27,000.

Examining the patients in the BMI group 17 to <20 kg/m\textsuperscript{2}, it was determined that the risk of dying was not statistically
different from the reference group. However, their LOS (ICU) tended to statistical significance (p=0.0626) compared to the reference group. This indicates that these patients were not dying more than the adequately nourished group, but they were in the ICU longer. From a cost perspective, this translates to an additional cost of $3000/patient \times 56 \text{ patients} = \$168,000.

Within the BMI >25 to 27 kg/m$^2$ group, patients had a significantly increased mortality and morbidity. This eight day difference (13 days versus 5 days) translates into $12,000 \text{ per patient} \times 19 \text{ patients} = \$228,000.

Patients within the BMI >27 kg/m$^2$ category also represented a significant problem both from a mortality and morbidity standpoint. This would represent an additional cost of $9000 \times 36 \text{ patients} = \$333,000.

It is apparent that the lung transplant patients with a BMI >27 kg/m$^2$ have an increased risk of mortality and morbidity, which appears to support the hypothesis. Thus, achieving a more healthy pre-transplant weight range, could potentially save the hospital 0.75 million dollars by reducing the patients' LOS (ICU).
For the reference category, the median LOS (H) was 25 days. This is similar to another report, where average stay in the hospital was reported to be 26 days, with a median of 22 days.\textsuperscript{90} Despite the fact that in the present study, the LOS (H) was not statistically different, the pattern closely follows the relationship seen in the LOS (ICU) and mortality results. If the cost of the additional days were examined, over and above the reference group, increased hospital costs would be seen.

For patients with BMI $<17$ kg/m$^2$ the median length of stay was 32 days, representing a difference of $2415$ per patient $\times 18$ patients = $43,470$. For the BMI group $17$ to $<20$ kg/m$^2$, the difference between the median of 25 days versus the median of 33 days is reflected in an additional cost of $154,560$. Patients within the BMI group $>25$ to $27$ kg/m$^2$, median 32 days versus the reference of 25 days, the additional cost would be $65,550$. Patients within the BMI group $>27$ kg/m$^2$, comparing the median of 25 days for the reference group versus the median of 34 days, the additional cost would be $111,780$. The total cost of reducing hospital stay by attempting to achieve a normal BMI is $375,360$. 
This research has reported that patients with an altered BMI have the highest mortality rate, the greatest length of time in the ICU, and the longest time in the hospital. This is in agreement with what was hypothesized. Between the length of stay in the ICU and the length of stay in the hospital there is a possibility of a total cost savings of ~$1.5 Million.
4.2. LIMITATIONS OF THE STUDY

This study is limited by the fact that the estimates were obtained from relatively small numbers of deaths. Hence, some P-values are close to statistical significance and the risk estimates may be unstable. It was believed that if the results were to be reproduced in a larger sample size, for example a multi-center study, BMI may become an important selection criterion or measure of risk in the assessment of a potential lung transplant candidate.

Another limitation of our study was that if this had been a prospective study, we would have been able to report episodes of infections. This could have further validated our study as the literature reports infectious episodes as the major cause of death in the lung transplant population. However, since this was a retrospective cohort study it would have been difficult to ascertain infectious episodes. To do so would require the need to document if the infections were confirmed with positive blood cultures, tissues, or respiratory secretions. For this to be accomplished completely and accurately would require a prospective study.
Acute rejection can be defined by histological criteria, as set out by the Lung Rejection Study Group.\textsuperscript{108} However, the present research did not confirm rejection by histological means, only if solumedrol was given, as documented in the chart. In some cases the clinical signs and symptoms are similar for infection or rejection, and patients may have been given a bolus of solumedrol because the clinical impression was that of rejection. Transbronchial biopsy would enhance the ability to diagnose rejection,\textsuperscript{109} however, the utility of this test is controversial as the sensitivity in diagnosing rejection is low.\textsuperscript{110}

It should be noted that throughout the study period, there have been many changes in discharge policies which may have changed or affected the LOS (ICU) and/or LOS (H) thereby altering the significance of some of the data.

Furthermore, no attempt to validate the prediction value of this model was done.
CHAPTER 5. SUMMARY AND CONCLUSIONS

5.1. SUMMARY

Using BMI 20-25 kg/m² as the reference category, our data indicated that for lung transplant patients with BMI values below 17 kg/m² there was a trend towards an increased 90 day mortality and no increased length of stay in the ICU or hospital.

For those patients with BMI between 17 to <20 kg/m² no increase in mortality was seen, but the LOS (ICU) tended to statistical significance and there was no increase LOS (H).

For Patients with BMI >25 to 27 kg/m² there was trend to statistical significance for 90 day mortality, a significant increase in LOS in ICU and no increase LOS (H). Patients with BMI >27 kg/m², had a statistically significant increased risk of mortality, and a significant increased LOS (ICU) and no increase in LOS (H).

For rejection episodes, there was no difference based on BMI categories in the number of patients who presented with acute rejection within the first 90 days. However, we observed a lower percentage of patients with rejection in the BMI <17 kg/m².
category (not significant). This may suggest a possible suppressive effect of malnutrition on immune function.

5.2. CONCLUSIONS

A pre-transplant BMI >27kg/m² was found to be a predictor of morbidity and mortality in ESLD patients post-transplantation. A low BMI showed an increased trend to morbidity and mortality; however, further studies are required to evaluate this possible relationship.
CHAPTER 6. REFERENCES

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