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Research Article

Obesity and the Outcome of Surgical Intensive Care Unit Patients: A Prospective Cohort Study

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2. Keywords

Obesity; Intensive Care Unit; Critical Illness; APACHI II Score; Mortality; Length of Hospital Stay

1. Abstract

1.1. Introduction: There is steady increase in prevalence of obesity over last 2-3 decades to the extent of global epidemic. Overall 25% of world population is reported to be overweight and 10% are obese. The evolutionary origin of obesity points towards survival advantage of obese individuals, but with modern ways of living, advantages of obesity are lost and hazardous effects have become more predominant. There is very scant information in medical literature about value of fat stores in critically ill patients; therefore the present study objective was to measure the impact of obesity upon mortality rate in patients admitted in surgical intensive care unit.

1.2. Methodology: This was a prospective cohort study conducted in Intensive Care Unit (ICU) of Aga Khan University Hospital Karachi, Pakistan. All adult patients of both gender and age > 16 years were eligible for inclusion in this study. Patients with diagnosis of malignant diseases, those shifted to other hospitals and patients with ICU stay of < 24 hours were excluded from the study group.

1.3. Results: A prospective data of 260 patients admitted to ICU was gathered. The mean age of the study population was 48.29 +/- 18.97 years. There were 172 (66.2%) male and 88 (33.8%) females in the study group. BMI was calculated for all patients; 35% were over-weight and 40% were in obesity class. Overall ICU mortality was 48.5%. Upon multivariate logistic regression analysis BMI and APACHE score turned out to be independent variables to predict mortality.

1.4. Conclusion: Risk of mortality of critically ill patients admitted to surgical intensive care unit in obese individuals as defined by BMI >27.5 is 1.4 times higher than the risk of mortality of same group of patients who are non-obese, adjusting for critically illness of patients as measured by APACHE II score.

3. Introduction

There is a steady increase in prevalence of obesity over last 2-3 decades to the extent of global epidemic [1,2]. Overall 25% of world population is reported to be overweight and 10% are obese [3]. It is known to be the cause of higher prevalence of cardio metabolic risk factors including diabetes mellitus, hypertension and hyperlipidemia [4,5] and certain malignancies [6,7]. It is also known to be an independent risk factor for all-cause mortality [8]. At least 2.8 million people die each year as a result of being overweight or obese. In addition, 44% of the diabetes burden, 23% of the ischemic heart disease burden and between 7% and 41% of certain cancer burdens are attributable to obesity [9]. According to one report, one in every four individuals in Pakistan is either overweight or obese [10].

The evolutionary origin of obesity on principle of "survival of the fittest" by Darwin points towards survival advantage obese individuals would have had over their non-obese counter parts to endure through labor intensive and injury prone life [11]. However, with more civilized ways of living there is increased food security, less physical work owing to machines and technology, and rare combat related injuries. Due to this change in environ-

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ment alongside the acquired genes continuing to be transferred to next generations, advantages of obesity are lost and hazardous effects have become more prominent including cardio-metabolic risk factors and certain malignancies [12,13]. On the other hand, hospitalized critically ill patients have increased metabolic and immune requirements as compared to those of healthy individuals. To meet these energy requirements, fat stores can potentially play an important role. It has been seen that increased levels of leptin in the body secondary to increased fat stores is known to strengthen the immune response and is associated with better sepsis outcome [14]. There is very scant literature about value of fat stores in critically ill patients. Some of studies have shown that obese individuals are not at increased risk of morbidity or mortality [15-17], while there are reports that have shown even protective effect of obesity in critical illness [18,19]. On the other hand, there are a few other reports that have shown obesity to be a risk factor for increased morbidity or mortality [20]. A meta-analysis of related studies was also conducted in 2008 by Akinnusi ME et al. [21]. They found that obesity in critically ill patients is not associated with excess mortality but is significantly related to prolonged duration of mechanical ventilation and intensive care unit length of stay. However most of these studies are either of retrospective nature or are secondary analysis of data collected for some other purposes. There is no conclusive evidence available as yet to conclude about impact of obesity upon outcome of critically ill patients. Knowledge obtained can be used in risk stratification and prognosis estimation of critically ill obese patients.

4. Objectives

4.1. Primary objective

To measure impact of obesity as measure by Waist Circumference and Body Mass Index, upon mortality rate of surgical intensive care unit patients.

4.2. Secondary objectives

To measure impact of obesity as measure by Waist Circumference and Body Mass Index, upon ICU stay of surgical intensive care unit patients.

5. Study Design

We conducted prospective cohort study. Patients were divided into two cohorts based upon their waist circumference values. Exposed cohort included the patients with waist circumference >85 cm for men and >80 cm for women, while non-exposed cohort included patients with waist circumference <85 cm for men and <80 cm for women [22]. All the patients included in the study were followed throughout their admission in intensive care unit till any of the outcomes was achieved or up to maximum of 90 days which was taken as censoring period. Patients were also was also categorized based upon Body Mass Index (BMI) values whereby obesity was defined as BMI >27.5.

6. Study Settings

Study was conducted at Intensive Care Unit (ICU) of Aga Khan University Hospital Karachi, Pakistan. Patients were recruited from surgical ICU. As the new patient's were admitted to surgical ICU, they were assessed according to predefined eligibility criteria. If they fulfilled the eligibility criteria, informed consent to participate in the study was taken from the patient or his/her first degree relatives. Surgical ICU at Aga Khan University Hospital (AKUH) is a twelve bed unit. Patients are managed primarily by anesthesiologist in consultation with respective surgical consultants.

7. Population

7.1. Target population

Our target population was critically ill adult patients admitted to surgical intensive care units.

7.2. Source population

Our source population was critically ill adult patients admitted to surgical intensive care unit at Aga Khan University Hospital (AKUH), Karachi, Pakistan. AKUH follows predefined internationally recognized criteria of admission to ICU. Critical illness of ICU patients is similar to the patients in ICUs around the world who follow the same or similar criteria.

7.3. Study sample

Our study sample was those critically ill adult patients admitted to surgical intensive care unit of Aga Khan University Hospital (AKUH) Karachi who fulfilled eligibility criteria and consent to participate in the study were granted.

8. Eligibility Criteria

All adult patients both males and females of age > 16 years admitted in Intensive Care Unit (ICU) of Age Khan Hospital Karachi were eligible for inclusion in study.

We included only 1st time admission to ICU in our study as recurrent admission can result in inclusion of a single patient multiple times in the study.

8.1. Exclusion criteria

• Malignancy

As obesity is a risk factor for certain malignancies. Also weight loss and cachexia associated with malignancy at the time of admission could lead to erroneous assessments of obesity that were not actually patients' baseline measurements. So patients diag-

nosed with or treated for any malignancy in the last ten years were excluded from study.

• Shifted out of Hospital

If patients were shifted out of hospital before reaching outcome, they were excluded.

• Transfer of patients to AKUH ICU from ICU of other hospitals

In these cases, patients usually have passed their initial 24 hour period when baseline assessment was to be done. Their parameters at time of admission to AKUH ICU would not be reflective of true parameters at the time of admission to ICU.

• ICU Stay < 24 Hours

ICU Stay less than 24 hours was not enough to measure all the parameters to calculate severity of illness.

9. Enrolment Procedure

Admission to Intensive Care Unit (ICU) can be from emergency, ward or operating room. After the admission, it takes about one hour for nursing staff to arrange all the monitoring devices and organize the medications and charts. We approached the patients after this time had lapsed and all the early measures to stabilize the patient had been taken. Patients were assessed for inclusion based upon eligibility questionnaire. If patient was conscious enough to understand nature of study, consent was taken from the patient and in case patient was not conscious enough to understand the nature of study, consent was taken from first degree relative as per hospital protocol.

10. Sampling Technique

We conducted non-probability consecutive sampling. All patients who met the selection criteria were offered to participate in the study. Data were collected on preformed questionnaire requiring information regarding demographics, exposure and outcome variables and co-variates.

11. Sample Size

Sample size was calculated using World Health Organization (WHO) software for both primary and secondary outcomes, keeping level of significance to be 5% and power of study to be 80%. Known mortality rate in surgical ICU was 30% [23]. A minimum of number of 121 patients were required in each group to detect a difference of 15% in mortality rate. Known mean length of ICU stay was 11 +/- 14.2 days [24]. A minimum of 105 patients were required in each group to detect a difference in ICU length of stay of 5 days. Total required minimum sample size was 242 patients. Accounting for 10% anticipated loss to follow up, we required at least 269 patients to be included in the study.

11.1. Measurement of Waist Circumference

Waist circumference was measured in centimeters using calibrated, non-stretch measurement tape. It was measured at level of mid-point from top of iliac crests to lower border of ribs on back [25]. It was recorded in expiration phase. Two measurements were taken at least five minutes apart and average of two was recorded as patient's value. In case difference between the two measurements was more than two centimeters, a third measurement was taken and mean of two closest readings was taken as patient's value. Ideally waist circumference should be measured in standing position. For purpose of our study, we were measuring the waist circumference in lying position as most of patients admitted to ICU in critically ill state were not able to stand or were not allowed to stand owing to their medical condition.

11.2. Measurement of BMI

Body Mass Index (BMI) was another measure of obesity that was used in our study. BMI was calculated by dividing weight in Kilograms by square of height taken in meters. Weight was taken as from the medical record. This was the weight of the patients taken by nursing staff at the time of admission to hospital. Weight of every patient was measured on a calibrated mechanical spring scale and was recorded in the patient's medical record at the time of admission. In case of non-ambulatory patients, weight was taken as a difference of weight of patients with wheel chair or stretcher and weight of wheel chair or stretcher. We took weight of patients at the time of admission because after admission multiple factors including resuscitation and intervention can modify the weight. Height of patients was taken as length in centimeters from vertex to sole. It was measured on a calibrated scale in standing position. In case patient was not able to stand, lying height was taken from vertex to soles.

11.3. Outcome Measures

11.3.1. Primary Outcome Variable (Mortality): Mortality was confirmed by team of doctors managing the clinical condition of the patient. For purpose of study, mortality was taken as mortality during ICU admission.

11.3.2. Secondary Outcome Variable (Length of ICU stay): If patients get better clinically, they are shifted out to lower level of care, usually high dependency units. Length of ICU stay was taken as number of days from ICU admission to shifting out of ICU.

12. Co-Variates

12.1. Severity of illness

Severity of Illness was assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II Score. APACHE II is a validated score to measure severity of illness in intensive care unit patients

[26].

12.2. Pretesting of questionnaire

Questionnaire was pretested on 5% of the study sample to check for any errors, difficulties encountered and logistic issues. Data collectors were trained and supervised by investigators.

13. Statistical Analysis

13.1. Descriptive Analysis

Qualitative variables including mortality are reported in percentages. Quantitative variables including length of ICU stay and APACHE II Score are reported in mean +/- standard deviation. Co-variates are reported for two groups.

13.2. Uni-variable Analysis

Univariate Cox-regression analysis is done for mortality as outcome and testing predictor variables ones by one.

Simple linear Regression analysis is done for length of ICU stay as outcome variable. T test is used to test significant difference. P value of less than 0.05 is considered significant.

13.3. Multivariable Analysis

13.3.1. Mortality: Multivariable Cox-regression analysis was done. P value of less than 0.2 at Univariable level was considered for inclusion into multivariable analysis which included BMI, Age, Hypertension and APACHE II severity score. Forward stepwise analysis was done. Variable of waist circumference being main predictor variable was kept in model. Other co-variates were added to the model in the order of their level of significance. Log likelihood ratio test was used to see significant improvement in the model.

13.3.2. Length of Hospital Stay: Multiple linear regression analysis was done. P value of less than 0.2 at Univariable level was considered for inclusion into multivariable analysis. Forward stepwise analysis was done. Variable of waist circumference being main predictor variable was kept in model. Other co-variates were added to the model in the order of their level of significance. F test was used to see significant improvement in the model.

13.4. Ethical Approval

Ethical approval was sought from Institutional Ethical Review Committee before start of study. ERC Number assigned is 3233-CHS-ERC-2014.

13.5. Potential Biases

13.5.1. Selection Bias: Obesity is a known risk factor for respiratory complications. Obese patient are at higher risk of requiring ventilator support so they are more likely to end up in ICU. This can result in potential selection bias in our study. To overcome this, we measured severity of illness of all the patients using APACHI II score which is a validated score to measure severity of illness in intensive care unit patients. At the time of analysis adjustments were done for severity of illness.

14. Results

Data was collected from November 01, 2015 till October 15, 2016. During the study period a total of 295 patients fulfilled the eligibility criteria out of which 11 refused to participate in the study and 24 patients were excluded due to incomplete follow up period. Data was analyzed for a total of 260 patients. Details are as given in **(Figure 1)**.

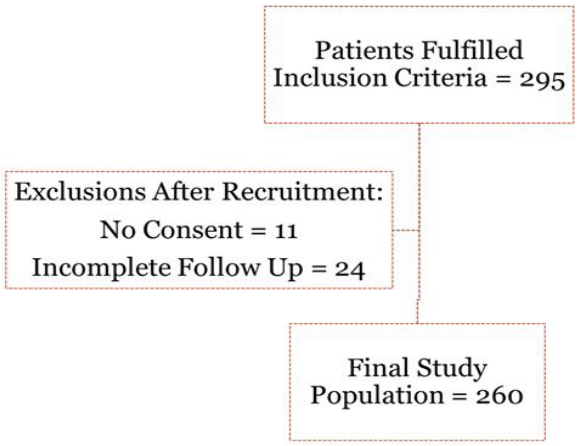

Figure 1: Flow Chart.

Mean age +/- Standard Deviation of our patients was 48.29 +/- 18.97 years. Out of total study population 172 (66.2%) were males and 88 (33.8%) were females. Our data showed that according to Waist Circumference, 91.2% of our study population was obese, while according to BMI 40.2% of study patients were obese. Details of obesity according to two criteria are shown in **(Table 1)**.

Table 1: Obesity Frequency according to Waist Circumference and BMI criteria.

Measure	Category	Number	Percentage
Waist Circumference	Obese (For Males >85CM, For Females > 80CM)	237	91.2
Body Mass Index	Normal (<22.99)	63	24.2
	Overweight (23-27.49)	92	35.4
	Obese (>27.5)	105	40.4

Table 2 gives details of distribution of co-variates amongst obese and non-obese patients as categorized by waist circumference. Mean APACHE II score was 14.21 +/- 10.86. Overall mortality in our study population was 48.5 % (126 patients). Mean length of ICU stay was 6.61 +/- 5.11 days.

Table 2: Distribution of co-variates amongst obese and non-obese patients.

Co-variates	Obese: n (%) or Mean +/- SD	Non-Obese: n (%) or Mean +/- SD
Age	48.64 +/- 18.33	44.74 +/- 24.91
Diabetes Mellitus	59 (24.9%)	3 (13%)
Hypertension	72 (30.4%)	8 (34%)
Ischemic Heart Disease	28 (11.8%)	4 (14.4%)
Emergency Admission / Operation	216 (91.1%)	19 (82.6%)
APACHE II Score	14.49 +/- 10.67	11.30 +/- 12.56

14.1. Uni-variable Analysis for Mortality

Univariate Cox regression analysis was done for mortality as outcome to calculate relative risk and predictor variables were tested ones by one. Results are reported in the form of a table as shown in **(Table 3)**. At Univariable level Age, BMI, HTN and APACHE II score turned out to be significantly associated with mortality.

Table 3: Univariable Cox-Regression Analysis with outcome as mortality.

Variable	Reference Category	Relative Risk	P Value	Log Likelihood
Waist Circumference	Non obese	.92	0.709	-180.02559
BMI	Non obese	1.29	0.041	**-177.98447**
Age		1.02	0.001	**-174.69807**
Gender	Male	.97	0.865	-180.08081
H/O DM	No	.85	0.264	-178.8051
H/O HTN	No	.74	0.028	**-177.63912**
H/O IHD	No	.79	0.190	-179.22233
Emergency Admission / Operation	No	1.08	0.710	-180.02588
APACHE II Score		1.03	0.000	**-170.35695**

14.2. Multivariable Analysis for Mortality

Multivariable Cox-regression analysis was done. P value of less than 0.2 at Univariable level was considered for inclusion into multivariable analysis which included BMI, Age, Hypertension and APACHE II severity score. Forward stepwise analysis was done. Variable of waist circumference being main predictor variable was kept in model. Other co-variates were added to the model in the order of their level of significance. Log likelihood ratio test was used to see significant improvement in the model. Upon multivariable Cox-regression analysis, BMI and APACHE score were the only variables independently predicting mortality.

14.3. Uni-variable Analysis for Length of ICU Stay

Simple linear Regression analysis was done for length of ICU stay as outcome variable. T test was used to test significant association. P value of less than 0.05 was considered significant. Only comorbidity with hypertension and ischemic heart disease turned out to be statistically significant. Results are shown in the **(Table 4)**.

Table 4: Simple linear Regression analysis with outcome as Length of ICU Stay.

Variable	Slope Co-efficient	MSE	R^2	F-test	p-value
Waist Circumference	.0449521	.042348697	0.0000	0.00	0.968
BMI	.9472705	55.8487263	0.0083	2.15	0.244
Mid-Arm Circumference	-.0893116	.510007134	0.0001	0.02	0.889
Age	.0220389	45.2930117	0.0067	1.74	0.288
Gender	-.1091839	.692622476	0.0001	0.03	0.871
H/O DM	5.532258	44.3095609	0.0132	1.71	0.282
H/O HTN	1.22095	82.4211773	0.0122	3.19	**0.075**
H/O IHD	2.873899	231.642891	0.0344	9.16	**0.003**
Emergency Admission / Operation	-.3916239	3.46413292	0.0005	0.13	0.716
APACHE II Score	.0026287	.209713519	0.0000	0.01	0.929

14.4. Multivariable Analysis for Length of ICU Stay

Multiple linear regression analysis was done. P value of less than 0.2 at Univariable level was considered for inclusion into multivariable analysis. Forward stepwise analysis was done. Variable of waist circumference being main predictor variable was kept in model. Other co-variates were added to the model in the order of their level of significance. F test were used to see significant improvement in the model. Only Ischemic Heart Disease turned out to be the independent predictor of ICU length of stay.

15. Discussion

Prevalence of obesity over last 2-3 decades has increased dramatically [1, 2]. Overall 25% of world population is overweight and 10% is obese [3]. It is known to be an independent risk factor for all-cause mortality [8]. Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. According to one report, one in every four individuals in Pakistan is either overweight or obese [10]. Our study done on critically ill patients in intensive care unit has demonstrated some interesting findings. Results show that obesity is an independent risk factor of mortality in critically ill patients. A few investigators have also reported impact of obesity upon outcome of critically ill patients with varying results. Some of these studies have shown that obese individuals are not at increased risk of morbidity or mortality [15-17]. Pieracci et al in retrospective review of their intensive care unit have shown that BMI is not associated with mortality. Similar results have been shown by Saker Y et al and Gupta R el al. There are reports that have shown protective effect of obesity in critical illness [18,19]. For example Hutagalung R et al reviewed outcome of their 13000 intensive care unit admission patients over a period of five year and found that being overweight or obese was associated with decreased 60-days in hospital mortality. Similarly Piake SL et al analyzed one year data of their intensive care unit patients. They found that BMI was determinant of short to medium term survival. They concluded that obesity was not associated with increased morbidity and could be

protective for critically ill patients.

Though we defined obesity as measured by both waist circumference and body mass index, a large number of study participants were not able to stand so waist circumference was measured inlaying position which is not ideal way how it should be. This is probably is underlying reason for more obsess patients if defined based upon waist circumference as opposed to when defined based upon body mass index. Also difference in outcome of mortality by two measures is due to limitation in accurate measurement of waist circumference. On the other hand, there are some studies that have shown obesity to be a risk factor for increased morbidity or mortality [20]. Duchesne JC et al reviewed one hundred and four trauma patients who were admitted to intensive care unit. They found that severe obesity was significantly associated with adverse outcomes and increased resource utilization in trauma patients treated admitted to ICU. Our results have shown that length of ICU stay is not affected by obesity. We took length of ICU stay as surrogate marker of morbidity. A meta-analysis of related studies was also conducted in 2008 by Akinnusi ME et al [21]. They analyzed fourteen studies having about sixty two thousand patients collectively. They found that obesity in critically ill patients is not associated with excess mortality but is significantly related to prolonged duration of mechanical ventilation and intensive care unit length of stay. Quality of life of patients who survive critical illness especially after trauma remains a concern but obesity is known to be associated with worse quality of life [27].

16. Conclusion

Risk of mortality of critically ill patients admitted to surgical intensive care unit in obese individuals as defined by BMI >27.5 is 1.4 times higher than the risk of mortality of same group of patients who are non-obese, adjusting for critically illness of patients as measured by APACHE II score.

17. Strengths

Ours is first ever prospective cohort study to look into impact of obesity upon outcome of critically ill patients in intensive care unit.

18. Limitations

Results of the study are generalizable to only critically ill patients. Study will have little generalizability to community at large. Measurement of Waist Circumference in lying position is not ideal but due to nature of study participants standing position was not feasible. Waist circumference in critically ill patients can also be in accurate due to body wall oedema.

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