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ASSESSING OUTCOME DISPARITIES AMONG CIRRHOTIC PATIENTS REQUIRING INVASIVE MECHANICAL VENTILATION FOR VARICEAL UPPER GASTROINTESTINAL BLEEDING: A CROSS-SECTIONAL STUDY

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Abstract:

Introduction: The global focus is on improving the quality of life for liver cirrhosis patients, particularly in low- and middle-income countries like Pakistan. It highlights the challenges in providing intensive care, including invasive mechanical ventilation, due to the increasing prevalence of liver cirrhosis. The study aims to examine outcomes for cirrhotic patients with upper GI bleeding requiring ICU care.

Methods: A cross-sectional study conducted in the Aga Khan University Hospital ICU in Karachi, Pakistan, from Jan to Nov 2016, focused on liver cirrhosis patients needing invasive mechanical ventilation. Data on patient characteristics, symptoms, hospitalization details, and outcomes, with exclusion criteria for specific conditions, were collected. Primary outcome was ICU mortality, wherease secondary outcome was differences in mortality based on various assessment scores. Statistical analysis was performed using SPSS, and significance was set at $p<0.05$.

Results: 88 patients were included in the final analysis. The median age was 52 years, with 65.1% males and 34.1% females. 31.8% were intubated due to variceal bleeding, with a 50% mortality rate among them. Common diagnoses included hepatitis C, non-B and non-C hepatitis, and hepatitis B,

with 79.5% requiring vasopressor support. Among the patients intubated due to excessive variceal bleeding, 50% died.
Conclusion: The study suggests cirrhosis patients needing invasive ventilation for upper GI bleeding fare better than those intubated for other reasons. Clinical parameters are crucial for prognosis. Multidisciplinary care is vital, involving hepatologists, intensivists, gastroenterologists, and critical care teams. Further research is needed to confirm findings and improve treatment strategies.

Keywords: Cirrhosis, Invasive Mechanical Ventilation, Variceal Bleeding

Introduction:

The notion of enhancing the health-related quality of life for patients afflicted with liver cirrhosis has seen global evolution, particularly in the past decade (1,2). However, the provision of effective healthcare in low- and middle-income countries (LMIC), such as Pakistan, where the prevalence of liver cirrhosis is notably high, remains a substantial challenge (3). This is exacerbated by the increasing prevalence of non-alcoholic fatty liver disease (NAFLD) in Pakistan, alongside existing chronic viral hepatitis B and C-related liver diseases, leading to a substantial number of patients developing liver cirrhosis (4,5). Liver cirrhosis induces immunosuppression, leading to significantly higher mortality rates when advanced and decompensated patients require hospitalization for acute emergencies and medical conditions (6,7). Additionally, these patients may necessitate escalated care, including vasopressor support, hemodialysis, or various forms of mechanical ventilation, both invasive and non-invasive (8). Often, liver transplantation remains the sole hope for these patients (9). Unfortunately, in LMIC like Pakistan, the liver transplantation process faces numerous challenges, from finding a suitable donor and the high cost of transplantation to the lack of financial support, particularly in the public sector, limited public awareness, and cultural and religious misconceptions surrounding the procedure (10,11). Consequently, many eligible candidates for liver transplant never reach the operating table and succumb to complications related to liver cirrhosis, such as decompensation following upper gastrointestinal (GI) bleeding, severe infections, sepsis, hepatorenal syndrome, acute kidney injury, hepatopulmonary syndrome, and multi-organ failure.
In recent years, there has been gradual progress in delivering intensive care and employing invasive mechanical ventilation for patients with complicated liver cirrhosis. Nevertheless, weaning these patients off the ventilator often presents considerable challenges. Nonetheless, some fortunate patients can successfully be extubated. Massive upper GI bleeding necessitating airway protection is one of the indications for maintaining these patients on invasive mechanical ventilation, followed by interventions for bleeding control (12). Acute variceal bleeding, if left uncontrolled, carries a high mortality (13). Previous studies have examined the outcomes of acute variceal bleeding compared to non-variceal bleeding in cirrhotic patients but have not specifically emphasized factors associated with mechanical ventilation in this population (14). Hence, it remains unclear whether cirrhotic individuals intubated for airway protection due to upper GI bleeding have distinct clinical outcomes in terms of extubation and ICU survival compared to those intubated for reasons unrelated to GI bleeding. This represents a gray area that warrants further investigation. Therefore, the primary objective of our study is to scrutinize the outcomes of cirrhotic patients requiring ICU care and invasive mechanical ventilation as a result of upper GI bleeding.

Methods:

Study design and setting

This cross-sectional study was conducted in the ICU setting of the Aga Khan University Hospital, Karachi, Pakistan, from January to November 2016. The results in this study are a secondary analysis of our already published work.

Study Participants
Patients aged ≥ 18 years with previously diagnosed liver cirrhosis, determined based on abdominal ultrasonography criteria (presence of coarse liver echotexture, irregular liver margins, and splenomegaly), and who required invasive mechanical ventilation were included.

Data Collection
The baseline characteristics of patients such as Gender, age, active alcohol intake, existing co-morbid illnesses, and etiology of cirrhosis were recorded. Additionally, we recorded symptoms such as syncope, melena, coffee ground vomitus, hematochezia, and hematemesis as well as details of hospitalization such as ICU stay, total length of stay, need for blood transfusions, utilization of inotropic agents, mechanical ventilation parameters, and occurrences of death during ICU stay were recorded on a predesigned proforma.

Exclusion Criteria
Patients with acute-on-chronic liver failure, acute coronary syndrome, and cerebrovascular accidents were excluded. Additionally, patient files with incomplete data and patients who left against medical advice or were transferred to another hospital due to a lack of ventilator availability were excluded from the final analysis.

Outcome Measures
The Primary outcome was ICU mortality. Secondary outcome was determining whether there was any difference in mortality among patients with GI bleeding with regards to the Child-Turcotte-Pugh (CTP), Model of End-stage Liver Disease (MELD), Acute Physiological Assessment and Chronic Health Evaluation (APACHE II), and Sequential Organ Failure Assessment (SOFA) scores.

Definition of Acute Variceal Bleeding (AVB)
AVB (acute variceal bleeding) was defined as the presence of varices on endoscopic assessment according to the Baveno IV-V criteria. Venous (non-pulsatile) bleeding, active bleeding at the gastroesophageal junction or gastric fundus in the presence of varices, or the presence of varices in the absence of other lesions suggested AVB (15).

Statistical Analysis
Statistical analysis was performed using the Statistical Package for Social Sciences SPSS version 17.0 for Windows (SPSS, Chicago, IL, USA). Categorical variables, such as gender, etiology of liver cirrhosis, presentation with an upper GI bleed, hepatic encephalopathy, urinary tract infection, and aspiration pneumonia, and quantitative variables, such as age, were reported as frequencies and percentages. Numeric variables were expressed as the mean and standard deviation during the descriptive analysis of the data. The chi-square test was applied to compare categorical variables Mann-Whitney U-Test. Applied to compare medians. A p-value of <0.05 was considered statistically significant.

Ethical considerations
We obtained an ethical exemption from the Ethical Review Committee (2521-Med-ERC-13) from Aga Khan University.

Results:
During the study period, 3502 patients were admitted to the ICU. Of these, 2246 (64.1%) required mechanical ventilation, and within this group, 490 (21.8%) had liver cirrhosis. Among the cirrhosis patients, 402 (82.0%) were excluded from the analysis, leaving 88 (18.0%) for inclusion (Figure 1).

The median age for all patients was 52 years, with an interquartile range (IQR) of 17.5 years. Of these patients, 58 (65.1%) were male, and 30 (34.1%) were female. Details of patients' characteristics are summarized in Table 1.Out of the 88 mechanically ventilated patients, 60 (68.2%) required it due to medical complications unrelated to GI bleeding, while 28 patients (31.8%) were intubated specifically because of excessive variceal bleeding. Common diagnoses included hepatitis C (52.3%), non-B and non-C hepatitis (18.2%), and hepatitis B (17.0%). Additionally, 70 patients (79.5%) required vasopressor support.Among the patients intubated due to excessive variceal bleeding, 50% died, while the remaining 50% survived. Table 2 compares intubated patients with GI bleeding and ICU mortality with those experiencing GI bleeding without ICU mortality.

Discussion:

In this study, the results indicate that out of the 88 mechanically ventilated patients, 31.8% were intubated specifically because of excessive variceal bleeding, while the rest were intubated due to medical complications unrelated to GI bleeding. The study also found common diagnoses among these patients, with the majority having hepatitis C, followed by non-B and non-C hepatitis, and hepatitis B. This is true for the Pakistani population as majority of the patients suffering from liver cirrhosis have underlying hepatitis C infection (16). Additionally, a significant number of patients required vasopressor support. The study revealed that patients with cirrhosis requiring invasive mechanical ventilation for upper gastrointestinal (GI) bleeding had a significantly lower mortality rate compared other studies where patients needed mechanical ventilation for other medical reasons, such as hepatic encephalopathy, cardiopulmonary compromise, or sepsis (8,17). Specifically, the study found that 50% of patients placed on invasive mechanical ventilation due to GI bleeding survived the event and were successfully extubated, while the remaining 50% did not. This outcome suggests that patients experiencing GI bleeding may have a more favorable prognosis when invasive mechanical ventilation is employed for airway protection in the context of upper GI bleeding. The relationship between variceal GI bleeding and ICU mortality has been looked into in the past by some authors. However, the jury is still out as to whether patients with acute variceal bleeding and requiring intensive care monitoring fare better as compared to those without GI bleeding. Annamalai et al. compared the clinical risk factors between cohorts of survivor and non-survivor liver cirrhosis patients who required ICU care. They found that the non-survivors had a considerably higher incidence of GI bleeding (17). On the other hand, another larger sample size albeit an older study by Cholongitas et al. elucidated that patients who had variceal GI bleeding upon admission to ICU were more likely to survive when compared to their non-bleeding counterparts (18). These findings were also endorsed by a recent meta-analysis that looked at ICU mortality of a pooled data of more than 300 patients (8). One study recently published states that decompensated cirrhotic patients intubated and put on invasive mechanical ventilation for hepatic encephalopathy of grade IV intensity, were managed in the intensive care setting early on the course of their admission, showed increased mortality and morbidity (19). Interestingly, none of the above studies specifically looked into the outcomes of patients with GI bleeding who were put on invasive mechanical ventilation. Our work precisely includes only those patients who required airway protection in the form of invasive mechanical ventilation, a characteristic which distinguishes our study from other similar studies. Furthermore, this study highlighted the significance of clinical parameters and scoring systems. Our previous work on cirrhotic patients requiring invasive mechanical ventilation showed MELD and CTP score to be superior in terms of predicting ICU mortality (20). In this study, we noted that a median CTP score of 11, MELD score of 20 and an APPACHE II score of 22 was associated with poor outcome in liver cirrhotic patients requiring invasive mechanical ventilation for bleeding indications**.** Moreover, prothrombin time (PT) was identified as a potentially independent predictor of mortality among critically ill GI patients with a history of bleeding, with higher PT levels observed among patients who did not survive. These results underscore the complexity of managing cirrhotic patients requiring ICU care and invasive

mechanical ventilation and suggest that specific clinical factors and scoring systems may play a crucial role in assessing and predicting patient outcomes in such cases.

The study's comparative approach, contrasting outcomes between those intubated for GI bleeding and those intubated for non-bleeding medical indications, adds depth to our understanding of the factors affecting patient survival. Furthermore, the examination of various clinical parameters and scoring systems like the MELD and PT enhances the study's comprehensiveness and the applicability of its findings in clinical practice. Additionally, the consideration of a prior study's results regarding MELD scores in cirrhotic patients requiring mechanical ventilation for non-bleeding indications adds to the context and supports the study's conclusions.

However, the study also has several limitations. Firstly, the relatively small sample size might limit the generalizability of its findings, and the study may not fully capture the diversity of cirrhotic patients requiring invasive mechanical ventilation. Secondly, the retrospective nature of the study might introduce bias or inaccuracies in data collection and analysis. The potential lack of certain variables and confounding factors that could affect outcomes, such as specific treatments or comorbidities, is another limitation. Moreover, the study's single-center design may not account for variations in clinical practices across different healthcare settings. While the findings suggest that invasive mechanical ventilation for GI bleeding may be associated with better outcomes, it is crucial to interpret these results with caution and consider these limitations when applying the study's conclusions to broader clinical contexts. The clinical implications of this study emphasize the need for a stratified approach to managing cirrhotic patients with upper gastrointestinal bleeding who require invasive mechanical ventilation. Healthcare providers should consider the underlying reason for intubation and incorporate the MELD score into patient assessment to predict outcomes and tailor treatment strategies, and a multidisciplinary care approach involving specialists from various fields should be employed (21). These findings underscore the importance of individualized patient care and call for further research to validate these conclusions and optimize the management and prognosis of this complex patient population. In conclusion, the study's findings suggest that patients with cirrhosis requiring invasive mechanical ventilation for airway protection during upper GI bleeding may have a more favorable outcome compared to those placed on invasive mechanical ventilation for other medical indications. However, the study also highlights the importance of clinical parameters when assessing the prognosis and management of these patients. Multidisciplinary care involving hepatologists, intensivists, gastroenterologists, and critical care teams should be standard practice for comprehensive patient management. Additionally, further research is needed to validate these findings and refine treatment strategies for this challenging patient population.

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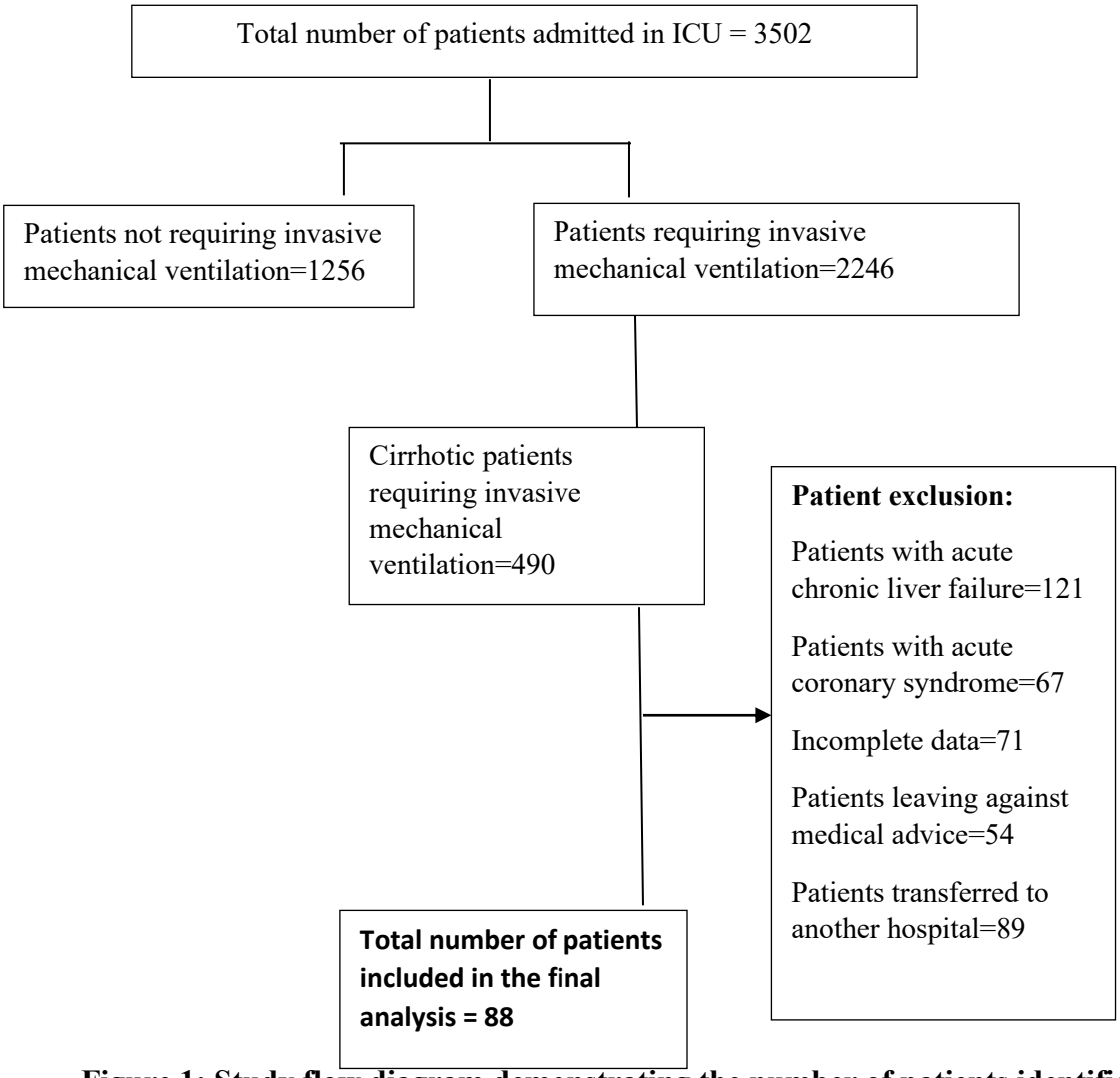

Figure 1: Study flow diagram demonstrating the number of patients identified

Table 1 : Distribution of demographic and health related characteristics among GI patients intubated and admitted in ICU of a private tertiary care hospital in Karachi (n=88)		
Variables	**Frequency (n)**	**Percentage (%)**
Age **Median age** 52 years (IQR=17.5) (20-40)years (41-60) years 61 years and above	 19 50 19	 21.6 56.8 21.6
Sex Male Female	 58 30	 65.1 34.1
Cirrhosis Etiology Hepatitis B Hepatitis C Alcohol abuse	 15 46 11	 17.0 52.3 12.5

Non-B Non-C hepatitis	16	18.2
Co-morbid		
Diabetes	34	38.6
Hypertension	28	31.8
Ischemic Heart Disease	12	13.6
Reason for intubation		
GI bleeding	28	31.8
Cardiac Arrest	2	2.3
Hepatic Encephalopathy	23	26.1
Respiratory Failure	14	15.9
Sepsis	21	23.9
Hepatic Encephalopathy		
Grade I-II	27	30.7
Grade III-1V	27	30.7
No	34	38.6
Hepatorenal syndrome		
Yes	27	30.7
No	61	69.3
Spontaneous bacterial peritonitis		
Yes	22	25.0
No	66	75.0
Urinary tract infection		
Yes	23	25.0
No	65	75.0
Pneumonia		
Yes	18	20.5
No	70	79.5
Concomitant hepatocellular carcinoma		
Yes	10	11.4
No	78	88.6
Need for dialysis		
Yes	10	11.4
No	78	88.6
Need for Vasopressor Support		
Yes	70	79.5
No	18	20.5

Table 2 : Comparison of various clinical and biochemical parameters among critically ill patients with history of GI bleeding with and without ICU mortality (n=21)

Variables	**Expired (n=14)**	**Discharged (n=14)**	***p-value**
	Median (IQR)		
Mean arterial pressure (MAP)	66.0(25.0)	72.5(22.0)	0.706
Hemoglobin levels	7.8(2.5)	8.0(1.7)	1.0
Peripheral Leucocyte Count	11.0(10.9)	7.5(5.7)	0.706
Platelet Count	77.5(99.7)	78.5(52.5)	1.0
Total bilirubin (mg/dl)	2.7(1.28)	1.6(0.75)	0.057
Serum Albumin (gm/dl)	1.9(0.7)	2.9(0.63)	0.007
Prothrombin time (sec)	21.0(6.7)	15.0(6.0)	0.006
Serum creatinine (mg/dl)	1.3(0.9)	1.05(0.3)	0.252

Serum Sodium	137.0(18.5)	132.5(10.2)	0.706
Serum Potassium	4.3(1.7)	4.1(1.2)	0.706
Serum Bicarbonate	16.0(8.7)	19.2(2.2)	0.236
Average duration of Hospital Stay /(in days)	7.0(4.7)	10.0(3.0)	0.054
Average duration of Mechanical Ventilation (in days)	4.0(3.5)	3.5(2.2)	0.420
CTP (Child-Turcotte-Pugh) Score (day 1 of MV)	11.0(3.5)	7.0(1.2)	0.007
MELD (Model of End-stage Liver Disease) Score (Day 1 of MV)	20.5(6.7)	12.5(4.0)	0.007
APACHE II Score (day 1 of MV)	22.5 (8.2)	13.5(6.2)	<0.001
SOFA Score (day 1 of MV)	10.0(6.2)	8.0(4.5)	0.120
**Mann Whitney-U test was applied. P-vale of 0.05 or less considered statistically significant.*			