**Trends, Management and Outcomes of Acute Myocardial Infarction in Chronic Liver Disease**

**Short title:** AMI outcomes in liver disease patients

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**Abstract:**

**Background:** Managing patients with chronic liver disease (CLD) that present with acute myocardial infarction (AMI) can be challenging. While there is limited data for CLD patients who develop AMI, sub-types of this heterogenous group have not been studied.

**Methods:** Using the Nationwide Inpatient Sample (2004-2015), we examined outcomes of AMI patients stratified by severity and sub-types of CLD. Multivariable logistic regression was used to determine the adjusted odds ratios (aOR) of invasive management and adverse outcomes.

**Results:** Out of 7,024,723 AMI admissions, a total of 54,283 (0.8%) had a CLD diagnosis. Patients with CLD were less likely to undergo coronary angiography (CA) and percutaneous coronary intervention (PCI) (aOR 0.74, 95%CI 0.72-0.76 and 0.72,0.70-0.73, respectively), and were associated with increased odds of adverse outcomes including major adverse cardiovascular and cerebrovascular events (1.13,1.09-1.18), mortality (1.26,1.20-1.31) and bleeding (1.57,1.51-1.64), compared with no-CLD. In comparison to the non-severe CLD sub-groups, severe patients had the lowest utilization of PCI, while severe alcohol liver disease (ALD) and ‘other CLD’ had the worst rates of mortality and bleeding (p<0.05). In the severe CLD category, ALD patients had the lowest utilization of PCI; patients with ALD and CLD from other causes had more adverse outcomes than viral hepatitis sub-group (p<0.05).

**Conclusions:** Patients with CLD are less likely to receive invasive management for AMI and are associated with an increased risk of adverse outcomes. Further disparities are observed depending on type of CLD, with the worse outcomes found in patients with severe ALD.

**Brief summary:**

This study examined the trends of management strategies and in-hospital outcomes of acute myocardial infarction in patients with chronic liver disease (CLD) and its subtypes in more than 7 million hospitalizations over a 12-year period. We found that CLD patients were less likely to receive invasive management, and were overall at an increased risk of adverse outcomes. The observed differences in management and outcomes were dependent on the etiology and disease severity.

**Introduction:**

Chronic liver disease (CLD) is a major cause of morbidity and mortality worldwide.1, 2 The most common causes of CLD are chronic viral hepatitis (hepatitis B and C), alcohol-related liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). With continued insult, the early stages of CLD can progress with worsening fibrosis, leading to cirrhosis and end-stage liver disease. Despite the stable prevalence of chronic viral hepatitis and ALD, the overall burden of CLD continues to increase, primarily due to a rise in the incidence of NAFLD, which is largely attributed to an increase in obesity and diabetes mellitus.1-3

Coronary artery disease (CAD) is common amongst patients with CLD, with an almost 37% prevalence in liver transplant recipients. 4-6 CLD patients presenting with acute myocardial infarction (AMI), pose a therapeutic dilemma for cardiologists. While their risk of cardiovascular mortality is at least as high as patients without CLD, they are at an inherent risk of major bleeding complications due to risk factors such as anemia, thrombocytopenia, decreased clotting factor synthesis, increased fibrinolysis and renal impairment.7-10 They may be less likely to receive guideline-recommended management in the form of percutaneous coronary intervention (PCI) and dual-antiplatelet therapy (DAPT) due to these increased risks.11-14 There is limited data on management strategies and clinical outcomes for this high-risk group when presenting with AMI from a national perspective. While there have been small studies on the utilization of invasive therapies and outcomes in a subset of such patients (e.g. ST-elevation myocardial infarction (STEMI) or AMI patients with cirrhosis),15, 16 these outcomes have not been systematically evaluated across CLD sub-groups.

Using the National Inpatient Sample (NIS), we examined the prevalence of CLD amongst patients presenting with AMI over a 12-year period, and evaluated differences in their receipt of invasive management and subsequent clinical outcomes, compared to patients without CLD, stratified by CLD severity as well as subtype.

**Methods**

*Data source*

The NIS is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality (AHRQ) which administers the Healthcare Cost and Utilization Project (HCUP).17 It includes anonymized data on primary and secondary discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset was designed to approximate 20% stratified sample of the US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. The estimates of hospital characteristics, numbers of discharges, length of stay and in-hospital mortality from the HCUP NIS for 2007 were highly comparable to three related data sources: the American Hospital Association Annual Survey Database, the National Hospital Discharge Survey from the National Center for Health Statistics, and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services (CMS). Furthermore, NIS was found to have a more comprehensive demographic capture when compared with a large multistate electronic health record (EHR) dataset in more than 25 diagnosis groups, including cardiovascular disorders.18 A recent validation study of the discharge diagnoses for AMI reported a high level of accuracy of ICD-9 codes (sensitivity and specificity of 98% and 91%, respectively).19

*Study design and population*

All hospitalized adults (≥18 years) with a principal discharge diagnosis of AMI between January 2004 and September 2015 were included. International Classification of Diseases, Ninth revision (ICD-9) and Clinical Classification Software (CCS) codes were used to identify patient comorbidities, procedures and clinical outcomes (Table S1). Additional comorbidities were identified using the existing 29 AHRQ Elixhauser comorbidity measures. Patient characteristics and clinical outcomes were stratified according to the presence or absence of CLD, and further by CLD subtype, into 3 groups; chronic viral hepatitis, ALD, other CLD diagnoses (Table S1). Finally, groups were stratified according to the disease severity (severe versus non-severe), based on the presence of portal hypertension, hepatic encephalopathy, hepatorenal syndrome and thrombocytopenia and coagulopathy. Cases excluded due to missing data for the variables *Hospital bedsize* and *Hospital location/teaching status,* and the presence of liver transplant represented 0.4% (n=28,752) of the original dataset (Figure S1). Before the exclusion of missing data, the dataset has been tested using Little’s MCAR test which showed completely random missingness pattern [Chi-square=1.985, DF=2, p=0.371]. These variables were kept in the analysis to allow for better understanding of the results and proper adjustment in the multivariable model.

*Outcomes*

 The main outcome was to compare the receipt of invasive management for AMI, in the form of coronary angiography (CA), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), and subsequent in-hospital clinical outcomes in patients with and without CLD. In-hospital complications included major adverse cardiovascular and cerebrovascular events (MACCE), all-cause mortality, major bleeding, cardiac complications and acute stroke. MACCE was defined as a composite of all-cause mortality, acute stroke/transient ischemic attack (TIA) and cardiac complications. Cardiac complications included hemopericardium, cardiac tamponade, coronary dissection and any pericardiocentesis procedure. All outcomes were based on in-hospital events/procedures irrespectively of the length of stay. However, almost all hospitalizations were shorter than 30 days (99.5%).

*Statistical analysis*

 We assessed the normality of data distribution by the Kolmogorov-Smirnov test. Data were expressed as median (interquartile range) for continuous non-parametric data and as numbers (percentages) for categorical data. Quantitative non-parametric data have been analysed with the Mann–Whitney U test and Kruskal-Wallis test, while the Chi-square test was used for the comparison of categorical variables between the study groups. Analyses were weighted by the provided discharge weights to allow estimation of national averages. All reported data were based on the weighted analyses as advised by HCUP.Statistical significance was defined at a level of p<0.05. SPSS 25 software (IBM Corp, Armonk, NY) was used for statistical analysis.

Multivariable logistic regression analysis was used to determine the adjusted odds ratios (aOR [95% confidence interval (CI)]) of adverse outcomes and the likelihood of an invasive management strategy in the total CLD cohort and different CLD subgroups, compared to the patients without CLD. The following variables were adjusted for in multivariable logistic regression analysis due to clinical importance and possible direct relation to the clinical outcomes: hospital factors: bed size of hospital, region of hospital, location/teaching status of hospital, and patient demographics: age, sex, weekend admission, primary expected payer, median household income, dyslipidaemia, smoking status, previous acute myocardial infarction, previous CABG, history of ischaemic heart disease, previous percutaneous coronary intervention, previous cerebrovascular accident, family history of coronary artery disease, cardiogenic shock or cardiac arrest during hospitalization, ventricular and atrial fibrillation, ventricular tachycardia and Elixhauser comorbidities (acquired immune deficiency syndrome, anaemia, chronic pulmonary disease, congestive heart failure, diabetes mellitus, drug abuse, fluid and electrolyte disorders, hypertension, hypothyroidism, lymphoma, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disorders, pulmonary circulation disorders, rheumatoid arthritis/collagen vascular diseases, solid tumour without metastasis, valvular heart disease, and weight loss). Except for the aforementioned variables, regression model for in-hospital clinical outcomes (MACCE, all-cause mortality, major bleeding, stroke) included PCI as a predictor variable.

A trend analysis has been conducted by assessing the interaction between CLD and time (years) on clinical outcomes in a logistic regression analysis. Furthemore, a Mantel-Haenszel test of trend (linear-by-linear association) was conducted in order to establish the trends of CLD rates in AMI hospitalizations over the 12-year time period.

**Results**

*Baseline Characteristics*

After excluding patients due to missing data (Figure S1), a total of 1,458,009 records of AMI between 2004 and September 2015 were identified, which corresponded to 7,024,723 hospitalizations. There were 6,970,440 patients (99.2%) in the no-CLD group and 54,283 patients (0.8%) in the CLD group. Figure 1 displays the trends of CLD rates in AMI hospitalizations. The rate of CLD amongst patients hospitalized for AMI has shown a steady increase and more than doubled from 2004 (0.5%) to 2015 (1.1%) (p<0.001 for trend). Figure 2 shows the proportion of patients in the different sub-groups of CLD; other causes accounted for most of these patients (0.4%), followed by chronic hepatitis (0.3%) and ALD (0.1%).

Demographics and comorbid conditions of the two groups are displayed in Table 1. Patients in the CLD group were more likely to be younger (median age 62 years in CLD group, 68 years in no-CLD group), male (65.8% in CLD group; 60.3% in no-CLD group), and have a higher prevalence of medical comorbidities including anemia, coagulopathy, chronic pulmonary disease, diabetes mellitus, drug abuse, fluid and electrolyte abnormalities, and renal failure. Patients without CLD had a higher percentage of dyslipidemia, family history of CAD, previous ischemic heart disease, prior AMI, prior PCI, prior CABG, previous CVA, and were more likely to present with STEMI.

*Management Strategy:*

Management strategies utilized in the groups are shown in Figure 3A and Table 2. Patients with CLD were less likely to undergo CA (57.5% versus 65.0%), PCI (31.9% versus 43.3%), CABG (8.6% versus 8.9%) and thrombolytic therapy (1.0% versus 1.4%) as compared with no-CLD. The CLD group was less likely to undergo CA and PCI (aOR 0.74; CI 0.72 to 0.76, p<0.001, and aOR 0.72; CI 0.70 to 0.73, p<0.001), respectively. (Table 3) Within the CLD subgroups, only patients with non-severe chronic viral hepatitis had similar rates of CA (aOR 0.93, CI 0.81 to 1.06, p=0.249) and PCI (aOR 0.89, CI 0.78 to 1.01, p=0.060) as patients without CLD, while other sub-groups were undertreated.

When comparing individual sub-groups of CLD based on severity, patients with severe form of other CLD and ALD had lower likelihood of CA and PCI compared to their non-severe counterparts, while severe and non-severe chronic viral hepatitis sub-groups differed only in receipt of PCI (p<0.05). Furthermore, amongst the severe sub-groups of CLD, patients with ALD had the lowest likelihood of PCI, followed by patients with other causes of CLD, while regarding receipt of CA patients with other CLD and ALD had similarly the worst rates (p<0.05).

*In-hospital outcomes:*

A comparison of overall rates of in-hospital outcomes are displayed in Figure 3B and Table 2. The rates of MACCE (8.4% in CLD group, 7.0% in no-CLD group), all-cause mortality (7.3% in CLD group, 5.7% in no-CLD group), major bleeding (4.7% in CLD group, 2.5% in no-CLD group), as well as the length of stay (median days 4 in CLD group, 3 in no-CLD group) were higher in patients with CLD. While the risk of cardiac complications was similar between the two groups (0.1%), patients with CLD had a lower rate of stroke (1.4% versus 1.5%) as compared to no-CLD.

Figure 4 shows a comparison of inpatient outcomes between the various subgroups of CLD, according to severity. Amongst the CLD subtypes, patients with severe forms of other CLD and ALD had higher rates of MACCE (17.4% vs. 7.4% and 15.4% vs. 12.3%), mortality (16.1% vs. 6.5% and 14.2% vs. 11.1%) and major bleeding (7.1% vs. 3.9% and 11.4% vs. 7.2%) compared to their non-severe counterparts, while severe chronic viral hepatitis sub-group showed lower rates of MACCE (6.3% vs. 7.9%), similar rates of mortality (5.0% vs. 6.0%) and higher rates of major bleeding (3.9% vs. 1.8%) in comparison to their non-severe equivalents.

The adjusted ORs of adverse events in the CLD group and the different CLD sub-groups are displayed in Table 3 and Figures 5-6. Patients with any CLD had a higher risk of MACCE (aOR 1.13, 95% CI 1.09-1.18), all-cause mortality (aOR 1.26, 95% CI 1.20-1.31) and major bleeding (aOR 1.57, 95% CI 1.51-1.64). However, the risk of stroke was lower in patients with CLD (aOR 0.79, CI 0.73-0.87).

When comparing sub-groups of CLD to no-CLD, most CLD sub-groups continued to have significantly higher likelihood of MACCE, mortality and major bleeding, except the non-severe chronic viral hepatitis sub-group which showed no difference in major bleeding (aOR 0.68, CI 0.45 to 1.02). Compared to no-CLD group, the odds of stroke was similar with most CLD subgroups , except in patients with non-severe CLD due to other causes (aOR 0.84, CI 0.75 to 0.94) and severe ALD (aOR 0.57, CI 0.36 to 0.90).

When comparing individual sub-groups of CLD based on severity, patients with severe form of CLD from other causes and ALD had higher likelihood of mortality and major bleeding compared to their non-severe counterparts, while higher likelihood of MACCE exhibited only sub-group with severe form of CLD from other causes (p<0.05). On the other hand, patients with severe form of chronic viral hepatitis had lower likelihood of MACCE and mortality, but higher risk of major bleeding, compared to non-severe subgroup (p<0.05). Furthermore, amongst the severe sub-groups of CLD, patients with CLD from other causes had the highest likelihood of MACCE and mortality, followed by patients with ALD, while both sub-groups of patients showed conjointly the highest risk of major bleeding (p<0.05).

Amongst patients who underwent PCI, those with CLD had a higher risk of MACCE (4.1% versus 3.6%), all-cause mortality (3.3% versus 2.9%) and major bleeding (3.9% versus 2.4%), but a lower rate of stroke (0.7% versus 0.8%) when compared with no-CLD (Table S2). Following adjustement for differences in baseline characteristics, adjusted ORs indicated that the risk was significantly higher only for MACCE (aOR 0.89, CI 0.80 to 0.99, p=0.028) and major bleeding (aOR 1.13, CI 1.02 to 1.25, p=0.020) in patients with CLD who underwent PCI; the risk of all-cause mortality was similar (aOR 1.00, CI 0.90 to 1.13, p=0.951), and the risk of stroke was lower (aOR 0.60, CI 0.48 to 0.76, p<0.001; Table S3).

The trends of adverse events are listed in Table S4 and further illustrated in Figure S2. Overall, there was a trend for a decline in the odds of MACCE (aOR 1.50 in 2004, 1.04 in 2015), all-cause mortality (aOR 1.61 in 2004, 1.13 in 2015) and stroke (aOR 1.31 in 2004, 0.70 in 2015) in patients with CLD compared to patients without CLD (p<0.001 for trend). The odds of major bleeding in patients with CLD compared to those without CLD has remained similar (aOR 1.49 in 2004, 1.15 in 2015) (p<0.001 for trend).

**Discussion:**

This is the first study to examine the prevalence, management strategy and clinical outcomes of CLD patients hospitalized for AMI from a nationwide perspective. This study shows that the prevalence of CLD among patients with AMI has doubled between 2004 and 2015. Patients with CLD were significantly less likely to receive invasive management for AMI compared to those without CLD, and were overall at a significantly increased risk of all-cause mortality as well as major complications including major bleeding. Additionally, we show that the differences in management strategies and outcomes of patients with CLD depend on the severity as well as the etiology. In comparison to their non-severe counterparts, severe CLD sub-groups had lower likelihood of PCI, while the severe form of CLD of other causes and ALD also showed higher mortality and major bleeding. In the severe disease patients, sub-group with ALD had the lowest likelihood of PCI, while patients with CLD of other causes had the highest risk of MACCE and mortality.

 The trends of CLD rates in patients presenting with AMI have not been systematically evaluated. This is the first, large scale evaluation demonstrating that the rates have steadily increased and doubled from 0.5% in 2004 to 1.1% in 2015. The rates of CLD in patients presenting with AMI in our study was similar to a prior, smaller analysis of the NIS (~10% sample size of the current study), that looked at cirrhosis alone and demonstrated a rate of approximately 0.5%.15 Based on epidemiological data, the increase in rate of CLD seen in our study over the years is likely related to an associated increase in the prevalence of NAFLD in the population.3

Patients with CLD that have AMI can pose a challenge to treating clinicians when considering invasive management strategies. A higher rate of the hematological derangements including anemia and coagulopathy can make the use of peri-procedural anticoagulation difficult. Additionally, these patients with a higher rate of renal dysfunction have an increased risk of developing contrast-induced nephropathy when undergoing invasive management. Expectedly, patients with cirrhosis and end-stage liver disease who undergo PCI and CABG have a higher risk of complications as well as mortality. 12-14, 20, 21 Similar to the findings seen in cirrhosis, patients with CLD have many of these co-morbidities and thus are also at an increased risk of complications. This can lead to a ‘risk-aversion’ tendency among treating physicians leading to lower utilization of invasive procedures in patients with CLD. Previous studies that focused on patients with AMI and cirrhosis15, 16 found that the utilization of invasive management is less in patients with cirrhosis. In this study, that included a larger group of patients with CLD, we show for the first time that the utilization of invasive management, including CA, PCI, CABG and thrombolytic therapy was lower in patients with CLD compared to those without CLD. Similar to findings in patients with end-stage liver diseae, we found that CLD patients undergoing PCI had worse MACCE and all cause bleeding, when compared to patients without CLD.

 This is the first study where differences in management between various sub-groups of CLD stratified by severity were analyzed. PCI was used the least among patients with severe forms of CLD with severe form of ALD showing the worst utilization as compared to other etiologies of CLD. There are many possible reasons for this. Stigmatization of patients that have alcohol dependence/abuse is a known phenomenon,22 and can lead to a lower utilization of invasive strategies. ALD patients can also present with withdrawal and delirium tremens, making the performance of invasive procedures difficult. Also, the rate of progression of liver disease with metabolic and hematological abnormalities, in general, is worse in patients with ALD compared to other CLD etiologies 23 and may preclude providers from performing invasive procedures more so in this sub-group. The progression of CLD from viral hepatitis is slower, leading to a relatively better hematological and metabolic profile in those with non-severe disease. This may explain why there was no difference in utilization of invasive strategies (CA and PCI) in patients with non-severe viral hepatitis related CLD when compared to patients without CLD.

 Prior smaller studies have shown worse outcomes including mortality in patients with cirrhosis and AMI,15, 16 and this large analysis shows similar findings in the larger group of patients with CLD. The higher risk of adverse events in patients with CLD could be related to many of the above-mentioned co-morbidities such as renal dysfunction and hematological derangements including thrombocytopenia, anemia and coagulopathy. Antiplatelet agents and statins, which form the mainstay of CAD and AMI therapy, are underutilized in patients with CLD.24 The utilization of invasive strategies has been associated with improved outcomes in this patient population,16 and its lower rate in patients with CLD is also a likely cause of worse outcomes. In addition, death from non-cardiac etiologies is more likely in patients with CLD which explains why patients who underwent PCI, the risk of mortality remained high.

Differences in outcomes among the various subgroups of CLD presenting with AMI were also evaluated for the first time in this study. In comparison to patients with non-severe disease, sub-groups with severe form of CLD of other causes and ALD have shown higher likelihood of mortality and major bleeding, while 23in the severe disease group, patients with ALD and other causes of CLD did much worse than patients with CLD from chronic hepatitis. Interestingly, while previous reports have shown that ALD could have a faster progression with worse metabolic and hematological derangements as compared to other causes of CLD23, our study has shown the worst mortality in patients with severe form of other CLD. This is emphasized even more given the finding of the worst utilization of PCI in patients with severe form of ALD. Based on known epidemiological data, patients in the other causes of CLD group most commonly have NAFLD with a small proportion of having other relatively rare diseases (such as hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, alpha-1-antitrypsin deficiency).3 NAFLD patients likely have a similar metabolic as well as inflammatory milieu that is seen in patients with CAD. It is likely that the ‘double-hit’ of cardio-metabolic syndrome and severe hepatic dysfunction contributed to worsened outcomes in this group. The lower rate of progression of CLD, relative lack of cardiometabolic risk factors and slighty more appropriate utilization of invasive strategies in patients with chronic hepatitis explains why outcomes in this group, while still worse than patients without CLD, were relatively better than other sub-groups of severe CLD.

The risk of major bleeding was higher in the overall group of patients with CLD, and highest amongst those with severe form of other CLD and ALD. This occurred despite a lower rate of utilizing invasive management (CA and PCI) in these patients, indicating that these patients had a high propensity for bleeding. Amongst patients who did undergo PCI in the CLD group, there was also a higher risk of bleeding compared to those without CLD. This underscores the importance of carefully weighing risks versus benefits of both medical (especially anticoagulation/antiplatelet agents) and invasive strategies in this high-risk group (especially in the ‘other CLD’ and ALD groups) presenting with AMI. Strategies such as radial access, use of less potent antithrombotic agents and third generation drug eluting stents that require short DAPT regimes would be considered when invasive strategy is planned.25-28

This study has several limitations that are inherent to the nature of analyzing data from an administrative dataset which is ICD code dependent and related to a specific hospitalization. There is always a possibility of misclassified, incomplete and omitted diagnoses or procedures. The specific etiologies of chronic hepatitis and other causes of CLD (eg. NAFLD) are unknown, given the limited ICD codes. Patients hospitalized with CLD are more likely to have a type 2 MI from etiologies such as sepsis, and associated vasodilatory shock.29, 30 It is possible that some of the patients in the CLD group of this study were such patients, and hence, it is expected that the role of invasive management, as well as overall adverse outcomes would be different in this group. The type of medical management (antiplatelet agents, anticoagulation) also plays an important role in outcomes; and are not captured for individual patients from this dataset.

In conclusion, this is the first large study to delineate trends in the rates of CLD in patients presenting with AMI, that has steadily increased and doubled over a decade. The rates of invasive management are lower, and that of most adverse events are higher in patients with CLD who present with AMI. Patients with severe form of ALD had the lowest rate of utilization of PCI, while MACCE, mortality and bleeding were worse in patients with severe form of ALD and CLD from other causes. Prospective evaluation of management strategies as well as longer term outcomes in the various sub-groups of patients with CLD presenting with AMI are needed.

**Disclosures**

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**Tables:**

**Table 1.** Patient characteristics of study groups

| **Variable/Group (%)** | **No CLD (99.2%)** | **CLD (0.8%)** | **p-value** |
| --- | --- | --- | --- |
| **Number of hospitalizations** | 6,970,440 | 54,283 |  |
| **Age (years), median (IQR)** | 68 (57, 79) | 62 (54, 71) | <0.001 |
| **Males, %** | 60.3 | 65.8 | <0.001 |
| **STEMI, %** | 29.4 | 20.1 | <0.001 |
| **Elective admission, %** | 7.0 | 5.6 | <0.001 |
| **Weekend admission, %** | 26.0 | 26.2 | 0.255 |
| **Primary expected payer, %** |  |  | <0.001 |
| **Medicare** | 57.4 | 51.6 |  |
| **Medicaid** | 6.0 | 14.0 |  |
| **Private Insurance** | 27.7 | 24.0 |  |
| **Self-pay** | 5.7 | 5.7 |  |
| **No charge** | 0.6 | 0.7 |  |
| **Other** | 2.7 | 4.1 |  |
| **Median Household Income Percentile, %** |  |  | <0.001 |
| **0-25th** | 28.6 | 31.2 |  |
| **26-50th** | 27.3 | 26.5 |  |
| **51-75th** | 23.8 | 22.4 |  |
| **76-100th** | 20.3 | 19.8 |  |
| **Cardiogenic shock, %** | 5.0 | 5.4 | 0.001 |
| **Cardiac arrest, %** | 1.6 | 1.9 | <0.001 |
| **Ventricular tachycardia, %** | 2.6 | 2.7 | 0.033 |
| **Ventricular fibrillation, %** | 2.7 | 2.3 | <0.001 |
| **Coronary dissection, %** | 0.5 | 0.5 | 0.874 |
| **Cardiac tamponade, %** | 0.1 | 0.0 | 0.024 |
| **Hemopericardium, %** | 0.0 | 0.0 | 0.329 |
| **Pericardiocentesis, %** | 0.0 | 0.0 | 0.996 |
| **Comorbidities, %** |  |  |  |
| **AF** | 16.6 | 16.6 | 0.854 |
| **Dyslipidaemia** | 55.1 | 44.8 | <0.001 |
| **Thrombocytopenia** | 2.3 | 12.3 | <0.001 |
| **Dementia** | 1.7 | 0.8 | <0.001 |
| **Smoking history** | 28.4 | 31.2 | <0.001 |
| **Previous AMI** | 8.6 | 7.7 | <0.001 |
| **History of IHD** | 76.9 | 69.6 | <0.001 |
| **Previous PCI** | 9.7 | 7.3 | <0.001 |
| **Previous CABG** | 6.1 | 4.3 | <0.001 |
| **Previous CVA** | 3.1 | 2.4 | <0.001 |
| **Family history of CAD** | 6.8 | 4.3 | <0.001 |
| **Deficiency anaemias** | 14.7 | 23.0 | <0.001 |
| **Chronic blood loss anaemia** | 1.1 | 2.4 | <0.001 |
| **Congestive heart failure** | 0.9 | 0.9 | 0.971 |
| **Chronic pulmonary disease** | 20.7 | 28.0 | <0.001 |
| **Coagulopathy** | 4.3 | 21.0 | <0.001 |
| **Depression** | 6.4 | 8.9 | <0.001 |
| **Diabetes** | 28.2 | 33.6 | <0.001 |
| **Diabetes with complications** | 6.1 | 9.8 | <0.001 |
| **Drug abuse** | 2.0 | 9.3 | <0.001 |
| **Hypertension** | 66.9 | 65.6 | <0.001 |
| **Hypothyroidism** | 9.8 | 10.0 | 0.126 |
| **Lymphomas** | 0.5 | 0.7 | <0.001 |
| **Fluid and electrolyte disturbances** | 19.3 | 30.1 | <0.001 |
| **Rheumatoid arthritis/collagen vascular diseases** | 2.2 | 2.6 | <0.001 |
| **Metastatic cancer** | 0.9 | 1.1 | <0.001 |
| **Other neurological disorders** | 5.8 | 6.7 | <0.001 |
| **Obesity** | 12.0 | 15.8 | <0.001 |
| **Paralysis** | 1.6 | 1.4 | <0.001 |
| **Peripheral vascular disease** | 10.9 | 12.2 | <0.001 |
| **Psychoses** | 2.1 | 4.5 | <0.001 |
| **Pulmonary circulation disorder** | 0.1 | 0.2 | <0.001 |
| **Renal failure (chronic)** | 16.7 | 24.0 | <0.001 |
| **Solid tumour without metastases** | 1.4 | 2.6 | <0.001 |
| **Ulcer disease** | 0.0 | 0.1 | <0.001 |
| **Valvular heart disease** | 0.2 | 0.3 | 0.001 |
| **AIDS** | 0.1 | 1.1 | <0.001 |
| **Weight loss** | 2.2 | 4.2 | <0.001 |
| **Hospital bed size, %** |  |  | <0.001 |
| **Small** | 10.7 | 9.7 |  |
| **Medium** | 24.9 | 24.7 |  |
| **Large** | 64.5 | 65.6 |  |
| **Hospital Region, %** |  |  | <0.001 |
| **Northeast** | 19.2 | 18.0 |  |
| **Midwest** | 23.3 | 18.9 |  |
| **South** | 40.0 | 40.0 |  |
| **West** | 17.5 | 23.1 |  |
| **Location/ Teaching status, %** |  |  | <0.001 |
| **Rural** | 10.2 | 8.1 |  |
| **Urban non-teaching** | 41.1 | 39.6 |  |
| **Urban- teaching** | 48.7 | 52.4 |  |

**Legend:** AF: atrial fibrillation; AIDS: acquired immunodeficiency syndrome; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CLD: chronic liver disease; CVA: cerebrovascular accident; IABP: intra-aortic balloon pump; IHD: ischemic heart disease; IQR: interquartile range; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

**Table 2.** In-hospital outcomes according to CLD and its subtypes

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **No CLD****(N=6,970,440; 99.4)** | **Total CLD (N=54,283; 0.8%)** | **p-value\*** | **Chronic viral hepatitis****(N=17,683; 0.3%)** | **Other CLD****(N=26,234; 0.4%)** | **Alcohol-related CLD****(N=10,366; 0.1%)** |
| **Non-severe****(7.4%)** | **Severe****(92.6%)** | **p-value†** | **Non-severe****(94.2%)** | **Severe****(5.8%)** | **p-value†** | **Non-severe****(84.2%)** | **Severe****(15.8%)** | **p-value†** |
| **MACCE, %** | 7.0 | 8.4 | <0.001 | 7.9 | 6.3 | 0.026 | 7.4 | 17.4 | <0.001 | 12.3 | 15.4 | 0.001 |
| **All-cause mortality, %** | 5.7 | 7.3 | <0.001 | 6.0 | 5.0 | 0.128 | 6.5 | 16.1 | <0.001 | 11.1 | 14.2 | <0.001 |
| **Major bleeding, %** | 2.5 | 4.7 | <0.001 | 1.8 | 3.9 | <0.001 | 3.9 | 7.1 | <0.001 | 7.2 | 11.4 | <0.001 |
| **Cardiac complications, %** | 0.1 | 0.1 | 0.056 | 0.0 | 0.0 | 0.573 | 0.1 | 0.3 | <0.001 | 0.1 | 0.0 | 0.289 |
| **Postprocedural haemorrhage, %** | 0.7 | 0.7 | 0.295 | 1.5 | 1.1 | 0.165 | 0.5 | 1.0 | 0.013 | 0.4 | 0.6 | 0.205 |
| **Stroke, %** | 1.5 | 1.4 | 0.026 | 1.9 | 1.4 | 0.161 | 1.2 | 1.3 | 0.731 | 1.7 | 1.2 | 0.092 |
| **CA, %** | 65.0 | 57.5 | <0.001 | 61.1 | 62.4 | 0.368 | 59.7 | 40.6 | <0.001 | 49.2 | 33.4 | <0.001 |
| **PCI, %** | 43.3 | 31.9 | <0.001 | 35.7 | 34.9 | 0.546 | 34.3 | 21.1 | <0.001 | 24.4 | 14.3 | <0.001 |
| **CABG, %** | 8.9 | 8.6 | 0.020 | 6.9 | 10.0 | <0.001 | 8.6 | 6.1 | 0.001 | 7.0 | 5.5 | 0.024 |
| **Thrombolysis, %** | 1.4 | 1.0 | <0.001 | 0.8 | 1.2 | 0.271 | 1.0 | 1.3 | 0.260 | 0.9 | 0.6 | 0.132 |
| **Use of IABP or assist device, %** | 4.9 | 4.2 | <0.001 | 3.1 | 4.5 | 0.013 | 3.7 | 4.0 | 0.600 | 5.2 | 3.4 | 0.002 |
| **Length of stay (days), median (IQR)** | 3 (2, 6) | 4 (2, 7) | <0.001 | 3 (2, 6) | 4 (2, 7) | 0.001 | 4 (2, 7) | 6 (3, 9) | <0.001 | 5 (3, 8) | 5 (3, 10) | <0.001 |

\*Comparison of no-CLD vs. total CLD group; †Comparison of subgroups based on severity within CLD subtype.

**Legend:** CA: coronary angiography; CABG: coronary artery bypass grafting; CLD: chronic liver disease; MACCE: major adverse cardiovascular and cerebrovascular events (composite of mortality, cardiac complications and stroke); PCI: percutaneous coronary intervention.

**Table 3.** Odds ratios (OR) of adverse complications and invasive management in the CLD group and different CLD subgroups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total CLD****(N=54,283; 0.8%)** | **Chronic viral hepatitis****(N=17,683; 0.3%)** | **Other CLD****(N=26,234; 0.4%)** | **Alcohol-related CLD****(N=10,366; 0.1%)** |
| **OR [95% CI]** | **Non-severe****(7.4%)** | **Severe****(92.6%)** | **Non-severe****(94.2%)** | **Severe****(5.8%)** | **Non-severe****(84.2%)** | **Severe****(15.8%)** |
| **OR [95% CI]** | **OR [95% CI]** | **OR [95% CI]** | **OR [95% CI]** | **OR [95% CI]** | **OR [95% CI]** |
| **MACCE** | 1.13 [1.09, 1.18] | 1.49 [1.20, 1.85] | 1.10 [1.03, 1.18]†§ | 1.18 [1.12, 1.24] | 2.44 [2.10, 2.83]†‡ | 1.73 [1.61, 1.86] | 2.17 [1.86, 2.52]‡§ |
| **Mortality** | 1.26 [1.20, 1.31] | 1.43 [1.12, 1.83] | 1.14 [1.06, 1.24]†§ | 1.30 [1.23, 1.38] | 2.82 [2.42, 3.29]†‡ | 2.00 [1.86, 2.17] | 2.68 [2.29, 3.14]†‡§ |
| **Bleeding** | 1.57 [1.51, 1.64] | 0.68 [0.45, 1.02] | 1.42 [1.31, 1.54]†§ | 1.42 [1.33, 1.51] | 1.85 [1.51, 2.26]†‡ | 1.99 [1.83, 2.17] | 2.92 [2.50, 3.42]†‡ |
| **Stroke** | 0.79 [0.73, 0.87] | 1.28 [0.83, 1.95] | 0.93 [0.81, 1.06] | 0.84 [0.75, 0.94] | 0.76 [0.48, 1.19] | 1.07 [0.91, 1.26] | 0.57 [0.36, 0.90]† |
| **CA** | 0.74 [0.72, 0.76] | 0.93 [0.81, 1.06] | 0.78 [0.76, 0.81]§ | 0.78 [0.75, 0.80] | 0.44 [0.39, 0.50]†‡ | 0.53 [0.51, 0.56] | 0.29 [0.26, 0.33]†‡ |
| **PCI** | 0.72 [0.70, 0.73] | 0.89 [0.78, 1.01] | 0.72 [0.70, 0.75]†§ | 0.75 [0.73, 0.77] | 0.52 [0.45, 0.59]†‡ | 0.50 [0.47, 0.52] | 0.29 [0.25, 0.34]†‡§ |

\*Reference group is no chronic liver disease; †Significant difference from non-severe CLD subtype; ‡Significant difference from severe chronic viral hepatitis subgroup; §Significant difference from severe other CLD subgroup.

**Legend:** CA: coronary angiography; CI: confidence interval; CLD: chronic liver disease; MACCE: major adverse cardiovascular and cerebrovascular events (composite of mortality, cardiac complications and stroke); PCI: percutaneous coronary intervention

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**Figure titles and legends:**

**Figure 1. Rate of CLD amongst AMI hospitalizations (2004-2015\*).**

**Legend:** \*2015 – 1st January through 30th September only; AMI – acute myocardial infarction; CLD – chronic liver disease.

**Figure 2. Frequency of different CLD subtypes in AMI population.**

**Legend:** AMI – acute myocardial infarction; CLD – chronic liver disease.

**Figure 3. Comparison between study groups: A. Invasive management; B. In-hospital outcomes.**

**Legend:** CA – Coronary Angiography; CA – Coronary Artery Bypass Grafting; CLD – chronic liver disease; MACCE – major adverse cardiovascular and cerebrovascular events (composite of mortality, cardiac complications and stroke); PCI – Percutaneous Coronary Intervention.

**Figure 4. In-hospital outcomes of different CLD subtypes based on disease severity.**

**Legend:** \*Presence of portal hypertension, hepatic encephalopathy, hepatorenal syndrome, thrombocytopenia and coagulopathy; CLD – chronic liver disease; MACCE – major adverse cardiovascular and cerebrovascular events (composite of mortality, cardiac complications and stroke).

**Figure 5. Adjusted odds ratios (OR) of adverse events in CLD group\*.**

**Legend:** \*reference is no CLD group; CLD – chronic liver disease; MACCE – major adverse cardiovascular and cerebrovascular events (composite of mortality, cardiac complications and stroke).

**Figure 6. Adjusted odds ratios (OR) of adverse events in different CLD subgroups\*: A. Non-severe CLD; B. Severe CLD†.**

**Legend:** \*reference is no CLD group; †Presence of portal hypertension, hepatic encephalopathy, hepatorenal syndrome and thrombocytopenia and coagulopathy; CA – Coronary Angiography; CLD – chronic liver disease; MACCE – major adverse cardiovascular and cerebrovascular events (composite of mortality, cardiac complications and stroke); PCI – Percutaneous Coronary Intervention.