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Liver enzymes in the emergency department and subsequent heart failure diagnosis: A real-world analysis of practice patterns and diagnostic value

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Abstract:

Background Abnormal liver biochemical and function tests (LFTs) are associated with increased mortality in patients hospitalized with acute decompensated heart failure (ADHF). However, there are no specific guidelines to inform clinical practice related to LFTs in the diagnostic work up of ADHF in the ED. Whether LFTs are ordered in the ED in patients with suspected ADHF and what additional diagnostic information they provide is unclear.

Objectives To determine (1) if LFTs are ordered in the ED in patients with suspected ADHF and (2) if the pattern of LFT abnormalities are meaningfully associated with a discharge diagnosis of ADHF among patients for whom these tests were ordered

Design We conducted a retrospective cohort study of patients with suspected ADHF seen in an academic emergency department using electronic medical records. We performed univariate and multivariate logistic regression to assess the association of LFT abnormalities with a final diagnosis of ADHF at hospital discharge.

Participants All ED patients admitted with suspected ADHF, defined as any patient who had a BNP ordered.

Results In 5,323 ED patients with suspected ADHF, 60% (n=3,184) had LFTs ordered; 34.6% were abnormal. The odds of a final diagnosis of ADHF in the univariate analysis was 59% higher in patients with abnormal LFTs (OR=1.59, p<0.001) and remained significant though attenuated after adjusting for BNP, race and ethnicity, and age (ORadj=1.31, p=0.004). Likelihood ratios (LRs) for abnormal and normal LFTs were 1.2 (95%CI: 1.21-1.28) and 0.76 (95%CI: 0.68-0.84), respectively.

Conclusions and Relevance A significant proportion (40%) of patients with suspected ADHF were missing LFTs in their ED workup. Among patients with LFTs, abnormal LFTs are associated with discharge diagnosis of ADHF after accounting for potential confounders, but their diagnostic value was relatively low. Future prospective studies are warranted to explore the role of LFTs in the workup of ADHF.

Strengths and Limitations of this study:

- Liver biochemical tests (LFTs) are commonly ordered in the emergency department; to our knowledge, this is the first study to evaluate the ordering behavior of providers in the ED in patients with suspected ADHF
- Guidelines suggest that LFT testing be considered in select cases, however, it is unclear what the utility of these tests are once they are ordered

- Although LFTs were associated with final diagnosis of ADHF, the diagnostic yield beyond biomarkers such as BNP was relatively low
- Our study does not evaluate the predictive value of LFTs in terms of outcomes such as all-cause mortality, but sets the framework for future investigation of this topic to avoid overuse of LFTs in ADHF in the ED

Introduction

Heart Failure (HF) is a leading cause of cardiovascular mortality, affecting 5.7 million Americans over the age of 20 from 2009-2012[1]. Projections show that the prevalence of HF will increase by 46% from 2012 to 2030[2], and disproportionately affect African Americans[7,8]. Despite newer treatments, mortality remains high[4,5,6].

Acute decompensated heart failure (ADHF) episodes lead to frequent emergency department (ED) visits among patients with HF. Additionally, readmission rates for ADHF are striking, with studies suggesting that 30-day and 180-day readmission rates approach 20-25% and 50%, respectively[9,10]. Although brain natriuretic peptide (BNP) has significantly improved the accuracy of ADHF diagnosis in the ED, patients are still misdiagnosed 10-20% of the time[11].

Liver function tests (LFTs) are commonly elevated in chronic heart failure[24] as a result of hemodynamic changes. However, LFTs have only more recently been studied as a predictor of heart failure prognosis during hospitalization for ADHF. The results of these studies have been varied with respect to individual LFT parameters[14,15,16,18], but seem to suggest that elevated LFTs are associated with worse prognosis. All of these studies were conducted in patients with a confirmed diagnosis of ADHF, where baseline LFTs are obtained on admission. Although

studies have explored LFT ordering patterns among ED providers,[21,22] LFTs have not specifically been examined in an ED population with suspected ADHF.

Heart failure is the most common and expensive reason for hospital admission for older Americans[29]. The American Heart Association's scientific statement on approaches to ADHF in the ED[30] recommends that LFTs should be considered in the work up of ADHF in select cases. The authors also emphasize that prior liver disease is an independent risk factor for worse mortality. However, surprisingly little research has been conducted in laboratory testing outside of routine BNP in patients with suspected ADHF in the ED and whether they offer additional diagnostic information. The lack of research in this area could lead to misuse of diagnostic tests, such as LFTs, and missed opportunities for early diagnosis in the ED.

Given the evidence for higher mortality in patients with ADHF and abnormal LFTs, it is necessary to assess if and how LFTs are utilized in the ED to inform the diagnosis of ADHF. Filling this gap in knowledge could potentially lead to an opportunity for earlier diagnosis, better resource utilization of laboratory testing and better risk stratification of ADHF. Using LFTs as an adjunct to BNP may also improve triaging of patients from the ED to appropriate levels of care. On the other hand, it is well known that overuse of tests in the ED does not improve outcomes[28]. In general, very little is understood about how ED providers use LFTs in their workup of ADHF in the first place, despite a large body of inpatient literature to suggest that abnormal LFTs can have prognostic value. This study aims to (1) evaluate the ordering patterns of LFTs in the ED in patients with suspected ADHF (2) in patients with LFTs, determine whether LFTs in an abnormal range obtained in the ED are associated with a higher likelihood of subsequent discharge diagnosis of ADHF.

Methods

We retrospectively identified all unique patient encounters seen in the ED at UCSF Medical Center between January 2017 and May 2018, and identified patients admitted to the hospital with suspected ADHF, defined as patients who had a BNP drawn in the ED. Among those patients, we analyzed the association between LFT ordering behavior and results, and the outcome of ADHF, defined by final discharge diagnosis.

Lab Measurements:

We extracted all measurements of BNP, alanine aminotransaminase [ALT], aspartate aminotransaminase [AST], alkaline phosphatase [AlkPhos], total bilirubin [TBili] and direct bilirubin [DBili] from the electronic health record between January 2017 and May 2018. Each LFT measurement was categorized into ranges representing normal, mild-moderate elevation, and significant elevation (or missing completely). These ranges were ALT <34, =34-99, >100 mg/dL or missing, AST <34, =34-99, >100 mg/dL or missing, AlkPhos <123, =123-199, >200 mg/dL or missing, and TBili <1.2, =1.2-2.0, >2.0 mg/dL or missing, and DBili was defined as DBili <0.3, =0.3-2.0, >2.0 mg/dL or missing. We also looked at a global LFT measurement, defined as abnormal if any of the LFT measurements were abnormal per patient encounter (i.e., any LFT parameter fell into the mild-moderate or significantly elevated categories), missing if all LFT measurements were missing per patient encounter, or normal if all LFT measurements were normal per patient encounter. If patients had more than one LFT parameter measured per unique encounter, we selected the most elevated value per encounter for the analysis.

Other predictors

We examined other predictors including age at ED admission, race and ethnicity. Race and ethnicity were categorized as non-Hispanic Asian, non-Hispanic Black or African American, non-Hispanic white, non-Hispanic other identified race (which included Native American or

other Pacific Islander, American Indian or Alaska Native, or patients who identified as "other race"), unknown or declined, or Hispanic, any race. BNP was categorized as high (>700 mg/dL), intermediate high (300-700 mg/dL), intermediate low (100-300 mg/dL), and low (<100 mg/dL).

Outcomes:

Because the diagnosis of ADHF is a clinical diagnosis[25], the final diagnosis given at discharge from the hospital was considered the "gold standard." We used any ADHF discharge diagnosis code (not just the first code) to define a final diagnosis of ADHF; see the Appendix for a listing of ICD-9 and ICD-10 codes we considered to indicate ADHF[27].

Statistical Analysis:

Baseline characteristics are presented as mean+/-SD for continuous variables and as frequencies and percentages for categorical variables. A p value of <0.05 was considered statistically significant and no adjustment was made for multiple comparisons. The data were analyzed with the use of commercially available statistical software (Stata, version 15).

To analyze the association between LFTs and ADHF, we first analyzed percentage of patients with an ADHF diagnosis according to categories of LFTs (and BNP) measurements. We used chi-square tests to evaluate these associations. We also calculated likelihood ratios (LRs) with 95% confidence intervals for each category of each predictor.

We then performed logistic regression to estimate the odds of final ADHF diagnosis for abnormal LFTs and each LFT parameter individually. We then adjusted analyses for BNP, age at ED visit and race and ethnicity.

Patient and Public Involvement:

No patient involved.

Results

LFTs were ordered in 60% of patients admitted from the ED with suspected ADHF (n=5323). Baseline characteristics are presented in Table 1. Mean age was 71+/-16 years in patients with normal LFTs, 67+/-16 in patients with abnormal LFTs and 68+/-16 years in patients with missing LFTs. An ED diagnosis of ADHF for patients with normal, abnormal and missing LFTs was 8%, 15% and 13% of patients, respectively. At hospital discharge (obtained per patient encounter), 21% of patients with normal LFTs were diagnosed with ADHF, compared to 30% of patients with abnormal LFTs and 29% of patients with missing LFTs.

Prevalence of Liver Function Tests:

For patients with suspected ADHF in the ED, LFTs were obtained in 60% of patients; 25% had normal LFTs and 35% had abnormal LFTs (40% were missing). Figure 1 demonstrates LFT ordering behavior across BNP subgroups and final diagnosis of ADHF. The likelihood of final diagnosis of ADHF among patients with abnormal LFTs was 1.8% for patients with missing BNP, 3.6% for patients with BNP<100 mg/dL, 15% for patients with BNP 100-300 mg/dL, 37% for patients with BNP 300-700 mg/dL and 54% for patients with BNP >700mg/dL.

Likelihood Ratios (LRs):

Table 2 demonstrates positive and negative LRs for any abnormal LFT and individual LFT parameters. Positive and negative LRs for abnormal LFTs in patients with suspected ADHF were 1.20 and 0.76, respectively. The LRs were similar for ALT, AST, AlkPhos, TBili and DBili. The positive and negative LRs were stronger for BNP, with LR of 2.95, 1.42, 0.51 and 0.13 for BNP>700, 300-700, 100-300 and <100 mg/dL.

Univariate and Multivariate Logistic Regression:

Table 3 demonstrates final diagnosis of ADHF in patients with normal, abnormal and missing LFTs. In the univariate analysis, the odds of a final diagnosis of ADHF were 59%

higher in patients with abnormal LFTs than those with normal LFTs (Odds ratio, OR 1.59 [Confidence Interval, CI 1.35-1.87] p<0.001). After adjusting for age, race and ethnicity, and BNP, this association remained statistically significant (OR 1.31 [CI 1.09-1.57] p=0.004).

Individual LFT measurements were also associated with ADHF. For example, abnormal TBili was associated with higher odds (OR 1.41 [CI 1.26-1.62] p=0.000) after adjustment, and this was seen at both very high (TBili >2mg/dL) and slightly elevated (TBili =1.2-2 mg/dL). Missing TBili was also positively associated with the final diagnosis of ADHF (OR 1.39 [CI 1.19-1.61], p=0.000). Odds ratios for other individual LFT parameters can be found in the Appendix (Appendix Tables 1-5).

We also conducted an interaction analysis by race and ethnicity variables. No statistically significant interactions were detected.

Discussion

The aim of this study was to conduct a real-world analysis of the LFT ordering patterns of providers in the ED and to determine whether abnormal LFTs help to predict ADHF as a final outcome diagnosis. Our study revealed that LFTs are not ordered as part of the work up for a substantial proportion of patients with suspected ADHF in the ED (40%) . The odds of a final diagnosis of ADHF was positively associated with abnormal LFTs, and of the individual LFT measurements, TBili had the highest odds (OR 1.41). Positive LRs for abnormal LFTs, both composite and individual measurements, were in the range of 1.0-1.3 and thus unlikely to be of much value for diagnosis of ADHF. We did not detect interactions by demographically-defined subgroups.

In an in-depth analysis of LFTs in suspected ADHF in the ED, our study makes several important observations that can inform future practice. First, a significant number of patients

with suspected ADHF had missing LFTs at this large tertiary center. Despite the AHA's scientific statement, nearly 40% of patients with suspected ADHF did not have LFTs ordered. This could be for a number of reasons, including lack of prior liver disease in the medical history to prompt ED providers to obtain LFTs or that sufficient diagnostic information was obtained through clinical history, imaging or BNP alone. Regardless of the reason, our study importantly suggest that despite the association of abnormal LFTs to higher mortality in patients with ADHF, ED providers are not routinely ordering LFTs in this subset of patients.

Second, in our analysis of patients who had LFTs, we discovered a positive association between abnormal LFTs and the odds of final diagnosis of ADHF in patients with suspected ADHF. These results are comparable to several landmark heart failure trials which examine prognosis in ADHF. ASCEND-HF, the largest study to date to explore this question, evaluated the relationship of baseline LFTs to 30-day and 180-day mortality in patients admitted for ADHF. Similar to our study, only 59% of patients had baseline LFTs. Elevated TBili was associated with a 24% and 30% increase in 30-day and 180-day mortality, respectively[31]. The authors found no association with AST or ALT. Another study found that abnormal ALT and AST values, as well as low albumin, have been associated with a combined endpoint of mortality or rehospitalization at 60 days[14]. Similarly, patients with ADHF had a high prevalence of abnormal LFTs at admission and was significantly associated with lower cardiac index and more elevated central venous pressures and MELD-XI scores[17]. However, both studies of baseline LFTs were inadequately powered to perform a multivariable analysis and did not account for other factors such as BNP. In the ED setting, making the diagnosis of ADHF is crucial to expediting treatment and thus reducing length of hospital stay and mortality[32].

Thus, to explore the true diagnostic value of these tests, we performed likelihood ratios which showed that the diagnostic value of these associations was relatively limited after adjustment for age, race and ethnicity, and BNP level, with LRs near 1.0. The LRs for BNP were strong: 2.95, 1.42, 0.51 and 0.13 for BNP>700, 300-700, 100-300 and <100 mg/dL. BNP and N-terminal pro-BNP have been shown to be effective in diagnosing ADHF because of their negative likelihood ratios, ranging from 0.1-0.14[26]. The LRs for BNP in our study were consistent with previous systematic reviews. To our knowledge, this is the first study to examine how LFTs predict ADHF in terms of LRs. The positive LR of 1.20 for abnormal LFTs and negative LR of 0.76 for normal LFTs that we found in our study are likely to have minimal diagnostic impact, especially when compared with the LRs for BNP.

In an era where value-based care is a major priority across hospital systems, it is important to critically assess the value of testing in the ED prior to admission. Studies such as the REDUCED trial[23] have examined the effects of uncoupling coagulation tests in the ED and found that implementing systemic changes to the order panel resulted in fewer tests ordered without a negative effect on patient outcomes. However, a clinical review[24] of the management of elevated LFTs in the ED suggested that severely elevated LFTs suggest injury secondary to cardiorenal syndrome and should prompt physicians to evaluate for ADHF. Although we found that the diagnostic utility of abnormal LFTs was relatively low, a significant proportion of patients with suspected ADHF did not have LFTs ordered. This might have impacted the diagnostic value of abnormal LFT findings in the ED setting. The presence or absence of a lab test itself has been shown in prior studies to be predictive of survival. In an analysis of all tests ordered between 2005 and 2006 at two hospitals, researchers found that the presence of a lab test order itself was significantly associated with the odds of survival in more than 80% of lab tests,

regardless of specific information related to the lab test itself[33]. This relates to our study in its key finding: the predictive value of healthcare process variables (guidelines, hospital metrics, the culture of how providers order tests at their institutions) might be more predictive of survival than the results of those tests themselves. We should undeniably strive to reduce unnecessary resource utilization in the ED. However, in ADHF, the high degree of mortality and costs related to advanced diagnostics such as echocardiogram renders further investigation of initial LFTs in the ED to inform guideline-directed practice. Prospective studies must be conducted to evaluate which patients would benefit from LFTs in terms of earlier diagnosis and risk stratification.

Our study has several limitations. First, this was a retrospective analysis of ED patients at a single site. We do not have baseline LFTs for this group of patients, so it is possible that patients with chronic HF had preexisting abnormal LFTs. Additionally, we did not systematically obtain LFTs for all potentially eligible patients, and a substantial number of patients did not have LFTs obtained in the ED. Patients with missing LFTs had higher odds of final ADHF diagnosis at discharge, similar to patients with abnormal LFTs. A plausible explanation for this finding is that ED clinicians were less likely to order LFTs if they had a high degree of certainty that a patient was presenting with ADHF. This finding makes it difficult to interpret the outcome in patients with missing LFTs, because these patients potentially might have had abnormal LFTs if the tests were obtained. However, it is important to note that other studies, such as ADHERE-HF, had similar proportions of missing LFTs to our study. This finding in itself is interesting in that it suggests that providers may have been relying more heavily on other forms of diagnostic testing, such as echocardiogram, when LFTs might have given a more cost effective insight into volume status or effective circulating volume. An important study done by Vyskocilova et al examined a large repository of patients with ADHF across 9 university hospitals and 5 regional

health care facilities in the Czech Republic. They found that abnormal LFTs were found in 76% of patients with ADHF and patients with cardiogenic shock were more likely to have abnormal LFTs than those with mild ADHF or pulmonary edema[34]. They found that abnormal LFTs were highly suggestive of more severe ADHF and reflected worse NYHA class. They argued that it is crucial to assess LFTs in the initial diagnostic investigation of ADHF as it informs management and stratifies patients based on severity. Although patients with missing LFTs were similarly diagnosed with ADHF to those with abnormal LFTs, it is possible that LFTs performed in the ED would have facilitated any additional work up performed after admission.

On the other hand, our study has important strengths, especially in contrast to prior analyses. First, we studied a large sample of patients seen in the ED prior to admission, where an initial suspicion for ADHF is most crucial to guide early evidence-based diagnosis and management. Second, our study was powered to adjust for BNP, which is known to be a strong predictor of ADHF. Third, our study estimated LRs, a key step in translating diagnostic test findings to clinical practice.

Our real-world analysis of patients admitted from the ED with suspected ADHF found that LFTs were not ordered for 40% of patients. Among patients who had LFTs ordered, abnormal LFTs in the ED are associated with a final ADHF diagnosis, the LRs indicate their limited diagnostic value, particularly in contrast with BNP. To balance the risks of overuse of tests and high inpatient mortality associated with abnormal LFTs, it is imperative to prospectively evaluate LFTs in the workup of ADHF and incorporate recommendations in society guidelines for clinical practice.

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Table 1. Baseline Characteristics of Patients with Suspected ADHF in the Emergency Department

Characteristic	LFTs – Normal Range N=1,342	LFTs - Abnormal Range N=1,842	LFTs – Missing N=2,139	P value[a]
Age at ED visit – mean in years+/-SD	71 +/-16	67 +/-16	68 +/-16	0.000
Sex Identified – No.(%)				
Male	633 (47%)	1,036 (56%)	1,113 (53%)	0.000
Female	709 (53%)	806 (44%)	1,026 (48%)	
Race and Ethnicity – No.(%)				
Non-Hispanic Asian	303 (23%)	459 (25%)	442 (21%)	0.000
Non-Hispanic Black or African American	236 (18%)	375 (20%)	401 (19%)	
Non-Hispanic White	546 (41%)	658 (36%)	918 (43%)	
Hispanic, any race	134 (10%)	202 (11%)	181 (9%)	
Other	108 (8%)	132 (7%)	174 (8%)	
Unknown/Declined to state	15 (1%)	16 (1%)	20 (1%)	
Insurance[b] No.(%)				
Private	147 (11%)	274 (13%)	295 (14%)	0.000
MediCal	218 (16%)	382 (21%)	367 (17%)	
Medicare	927 (69%)	1,086 (59%)	1,357 (64%)	
Other	49 (4%)	23 (1.3%)	117 (5%)	
Diuretics in the ED?				
Yes	250 (19%)	449 (24%)	483 (23%)	0.001
No	1,092 (81%)	1,393 (76%)	1,656 (77%)	
BNP* in the ED?				
High BNP (>700mg/dL)	308 (23%)	636 (35%)	618 (29%)	0.000
Intermediate High BNP(300-700mg/dL)	278 (21%)	357 (19%)	441 (21%)	
Intermediate Low BNP(100-300 mg/dL)	339 (25%)	376 (20%)	455 (21%)	
Low BNP (<100 mg/dL)	417 (31%)	473 (26%)	625 (29%)	

Past Medical History				
History of Asthma	251 (19%)	244 (13%)	379 (18%)	0.000
History of COPD	345 (26%)	412 (22%)	580 (27%)	0.002
History of Smoking	699 (52%)	928 (50%)	1,129 (53%)	0.012
ED Diagnosis**				
ADHF†	107 (8%)	274 (15%)	281 (13%)	0.000
Pneumonia	175 (13%)	243 (13%)	330 (15%)	0.025
COPD exacerbation	124 (9%)	96 (5%)	235 (11%)	0.000
Asthma exacerbation	27 (2%)	28 (2%)	68 (3%)	0.001
Acute Upper Respiratory Infection	2 (0.2%)	1 (0.1%)	8 (0.4%)	0.028
Any Liver Pathology‡	12 (1%)	107 (6%)	16 (1%)	0.000
Final Discharge Diagnosis°				
ADHF	283 (21%)	549 (30%)	622 (29%)	0.000
Not ADHF	1,059 (79%)	1,293 (70%)	1,517 (71%)	

[a]P values based on Chi Square analysis for categorical variables and ANOVA for continuous variables
[b]Insurance is categorized as "Private" (Aetna, Blue Cross, Blue Shield, GCSS/GHP, Capitation, Charity, Commercial, Covered California, Covered California – MediCal, HealthNet, Institutional, and Kaiser), "MediCal" (Medicaid/MIA/CMSP, MediCal managed care, MediCal pending, MediCal standard) "Medicare" (Medicare, Medicare Advantage HMO/Senior, Medicare Advantage PFFS) and "Other" (Self-pay, United Health Care, Worker's compensation)
*BNP=Brain Natriuretic Peptide
**ED Diagnosis was obtained through specification of ICD10 codes for respiratory diagnoses and liver-related diseases
†ADHF=Acute Decompensated Heart Failure
‡Any liver pathology includes ICD10 codes for the following: alcoholic liver disease, toxic liver disease, hepatic failure (not elsewhere specified), chronic hepatitis (not elsewhere specified), fibrosis and cirrhosis of liver, other inflammatory liver diseases, other diseases of the liver, liver disorders in diseases of the liver (classified elsewhere)
¶Suspected ADHF is defined as patients who had a BNP ordered in the ED
°Final discharge diagnosis of ADHF is based on ICD 10 codes for a diagnosis of heart failure named on the discharge summary for a patient's specific encounter

Table 2. Liver Function Tests, BNP and Acute Decompensated Heart Failure at Discharge in ED patients with suspected ADHF (n=5,323)

Characteristic	N	% with ADHF diagnosis at discharge	p-value*	LR(95% CI)
Liver Function Tests (LFTs)				
Abnormal LFTs	1,842	30%	0.000	1.20 (1.13-1.28)
Normal LFTs	1342	21%		0.76 (0.68-0.84)
Missing LFTs	2139	29%		-
Alanine Transaminase (ALT)				
ALT >=100 mg/dL	168	27%	0.017	1.03 (0.74-1.44)
ALT 34-99 mg/dL	684	30%		1.19 (1.03-1.37)
ALT <34 mg/dL	2,310	25%		0.95 (0.90-1.00)
Missing ALT	2,161	29%		-
Aspartate Transaminase (AST)				
AST>=100 mg/dL	246	24%	0.000	0.87 (0.66-1.16)
AST 34-99 mg/dL	1,070	30%		1.22 (1.10-1.35)
AST <34 mg/dL	1,864	24%		0.90 (0.84-0.97)
Missing AST	2,143	29%		-
Alkaline Phosphate (AlkPhos)				
AlkPhos >=200 mg/dL	249	22%	0.004	0.81 (0.60-1.08)
AlkPhos 123-199 mg/dL	420	31%		1.26 (1.04-1.53)
AlkPhos <123 mg/dL	2,451	26%		0.98 (0.94-1.02)
Missing AlkPhos	2,203	29%		-
Total Bilirubin				
Total Bilirubin>2mg/dL	323	32%	0.000	1.32 (1.06-1.65)
Total Bilirubin 1.2-2 mg/dL	501	36%		1.59 (1.35-1.88)
Total Bilirubin<1.2 mg/dL	2,314	23%		0.85 (0.81-0.90)

Missing Total Bilirubin	2,185	29%		-
Direct Bilirubin				
Direct Bilirubin>2 mg/dL	18	22%	0.007	0.62 (0.22-1.75)
Direct Bilirubin 0.3-2 mg/dL	48	48%		1.99 (1.32-3.00)
Direct Bilirubin<0.3 mg/dL	51	20%		0.53 (0.30-0.93)
Missing Direct Bilirubin	5,206	27%		-
BNP**				
High BNP (>700mg/dL)	1,562	53%	0.000	2.95(2.72-3.19)
Intermediate High BNP(300-700mg/dL)	1,076	35%		1.42(1.28-1.59)
Intermediate Low BNP(100-300 mg/dL)	1,170	16%		0.51(0.44-0.59)
Low BNP (<100 mg/dL)	1,515	5%		0.13(0.10-0.17)

*P-values are based on Chi-Square test
**BNP=Brain Natriuretic Peptide

Table 3. Univariate and Multivariate Logistic Regression Analysis of High LFTs and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5,323)

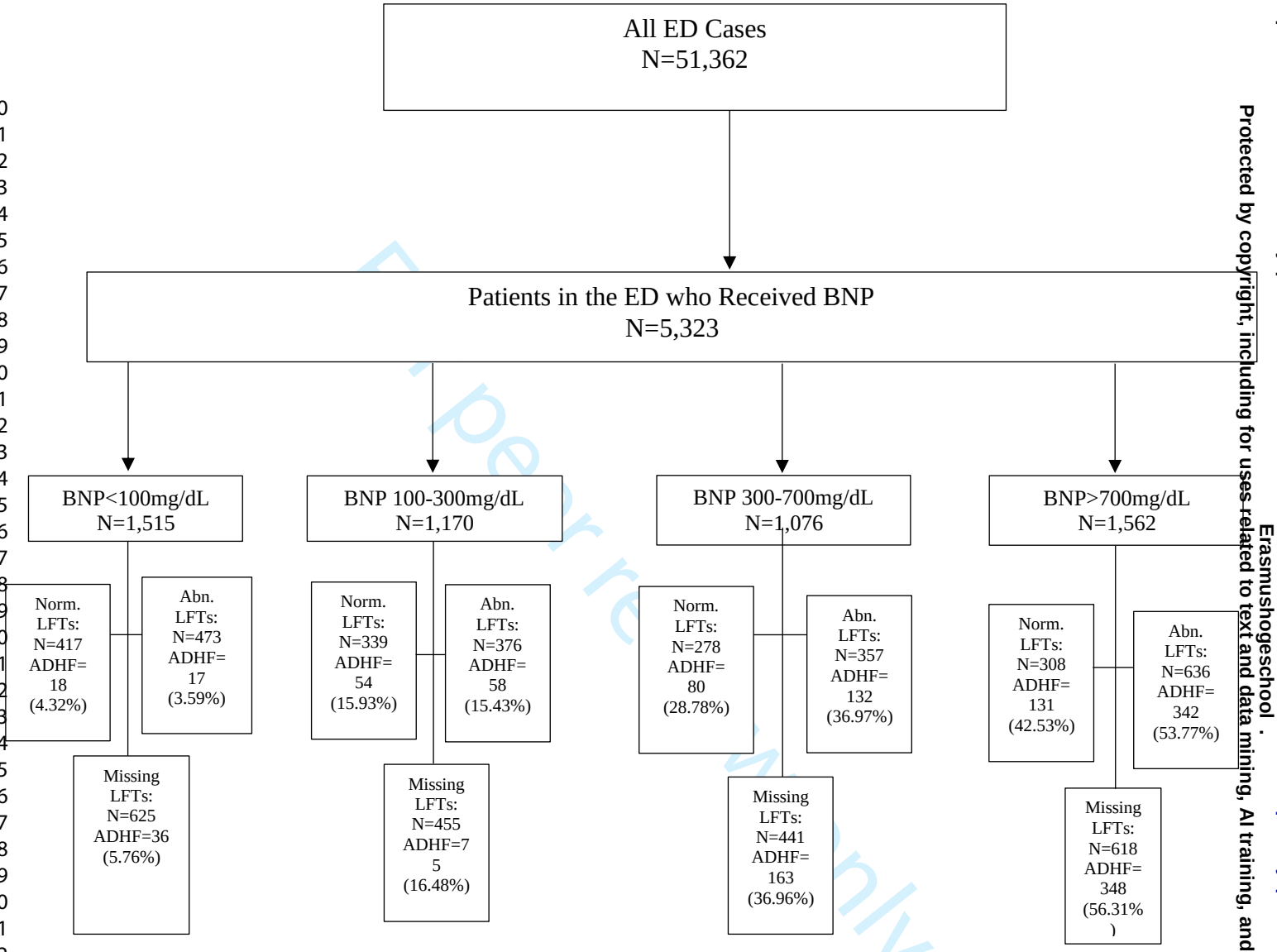
Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Abnormal LFTs	1.59(1.35-1.87)	0.000	1.31 (1.09-1.57)	0.004
Missing LFTs	1.53(1.31-1.80)	0.000	1.44 (1.20-1.72)	0.000
Normal LFTs	Reference	Reference	Reference	Reference
BNP**				
High BNP (>700mg/dL)	22.53(17.41-29.17)	0.000	22.76 (17.52-29.56)	0.000
Intermediate High BNP(300-700mg/dL)	10.88(8.31-14.24)	0.000	11.17 (8.49-14.68)	0.000
Intermediate Low BNP (100-300 mg/dL)	3.87(2.91-5.14)	0.000	4.00 (3.00-5.33)	0.000
Low BNP(100 mg/dL)	Reference	Reference	Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65-1.01)	0.064
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.94 (0.78-1.14)	0.515
Other, Non-Hispanic			1.06 (0.80-1.41)	0.695
Hispanic, any race			0.96 (0.73-1.25)	0.741
Unknown/Declined to state			0.53 (0.22-1.29)	0.162
Age at ED visit, per year			1.001 (0.99-1.00)	0.266

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Figure 1. Classification Tree



Appendix:

Appendix Table 1. Univariate and Multivariate Logistic Regression Analysis of High ALT and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	Univariate Analysis		Multivariate Analysis*	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
ALT>100 mg/dL	1.09(0.76-1.55)	0.638	1.01 (0.68-1.50)	0.958
ALT 34-99 mg/dL	1.26(1.04-1.52)	0.018	1.23 (1.00-1.52)	0.054
ALT<34 mg/dL	Reference	Reference	Reference	Reference
Missing ALT	1.21 (1.06-1.38)	0.005	1.26 (1.08 -1.46)	0.002
High BNP (>700mg/dL)			23.21 (17.87-30.14)	0.000
Intermediate High BNP(300-700mg/dL)			11.28 (8.58-14.82)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.03 (3.02-5.37)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65-1.01)	0.066
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.94 (0.77-1.13)	0.499
Other, Non-Hispanic			1.05 (0.79-1.40)	0.726
Hispanic, any race			0.96 (0.73-1.24)	0.739
Unknown/Declined to state			0.52 (0.21-1.26)	0.148
Age at ED visit			1.00 (0.99-1.00)	0.201

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 2. Univariate and Multivariate Logistic Regression Analysis of High AST and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
AST>100 mg/dL	0.97 (0.71-1.32)	0.831	1.02 (0.72-1.45)	0.914
AST 34-99 mg/dL	1.35 (1.15-1.60)	0.000	1.16 (0.96 -1.40)	0.116
AST<34 mg/dL	Reference	Reference	Reference	Reference
Missing AST	1.28 (1.11-1.48)	0.001	1.28 (1.10-1.50)	0.002
High BNP (>700mg/dL)			23.07 (17.76 - 29.96)	0.000
Intermediate High BNP(300-700mg/dL)			11.25 (8.56-14.79)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.02 (3.01-5.35)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.82 (0.66-1.02)	0.071
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.94 (0.78-1.14)	0.538
Other, Non-Hispanic			1.06 (0.80-1.41)	0.688
Hispanic, any race			0.96 (0.74-1.25)	0.774
Unknown/Declined to state			0.53 (0.22-1.28)	0.158
Age at ED visit			1.00 (0.99-1.00)	0.183

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 3. Univariate and Multivariate Logistic Regression Analysis of High AlkPhos and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)*

Characteristic	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
AlkPhos>200 mg/dL	0.82(0.60-1.13)	0.222	0.80 (0.56-1.12)	0.194
AlkPhos 123-199 mg/dL	1.29(1.03-1.61)	0.029	1.02 (0.79-1.31)	0.866
AlkPhos<123 mg/dL	Reference	Reference	Reference	Reference
Missing AlkPhos	1.19(1.05-1.36)	0.007	1.21 (1.04-1.39)	0.011
BNP**				
High BNP (>700mg/dL)			23.425 (17.90-30.21)	0.000
Intermediate High BNP(300-700mg/dL)			11.24 (8.55-14.77)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.01 (3.01-5.34)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.82 (0.66 -1.02)	0.080
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.94 (0.78-1.14)	0.522
Other, Non-Hispanic			1.06 (0.80 -1.41)	0.694
Hispanic, any race			0.95 (0.73-1.23)	0.690
Unknown/Declined to state			0.53 (0.22 -1.28)	0.159
Age at ED visit			1.00 (0.99-1.00)	0.143

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 4. Univariate and Multivariate Logistic Regression Analysis of High DBili and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
DBili>2 mg/dL	1.17(0.32-4.34)	0.813	1.41 (0.34-5.82)	0.635
DBili 0.3-2 mg/dL	3.77(1.54-9.22)	0.004	3.62 (1.32-9.94)	0.013
DBili<0.3 mg/dL	Reference	Reference	Reference	Reference
Missing DBili	1.53(0.77-3.07)	0.227	1.43 (0.67-3.04)	0.359
BNP**				
High BNP (>700mg/dL)			23.12 (17.80 - 30.03)	0.000
Intermediate High BNP(300-700mg/dL)			11.24 (8.55 - 14.77)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.02 (3.01-5.36)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65 -1.01)	0.064
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.94 (0.78-1.14)	0.532
Other, Non-Hispanic			1.05 (0.79-1.40)	0.717
Hispanic, any race			0.95 (0.73-1.23)	0.690
Unknown/Declined to state			0.52 (0.21-1.26)	0.146
Age at ED visit			1.00 (0.99-1.00)	0.044

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 5. Univariate and Multivariate Logistic Regression Analysis of High LFTs and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5,323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
TBili>2 mg/dL	1.55 (1.20-2.00)	0.001	1.39 (1.04-1.85)	0.024
TBili 1.2-2 mg/dL	1.87 (1.52-2.30)	0.000	1.41 (1.12-1.78)	0.003
TBili<1.2 mg/dL	Reference	Reference	Reference	Reference
Missing TBili	1.40 (1.22-1.60)	0.000	1.39 (1.19-1.61)	0.000
BNP				
High BNP (>700mg/dL)			22.72 (17.49 - 29.52)	0.000
Intermediate High BNP(300-700mg/dL)			11.19 (8.51 - 14.72)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.01 (3.00-5.34)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65 -1.01)	0.062
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.12)	0.438
Other, Non-Hispanic			1.05 (0.79-1.40)	0.714
Hispanic, any race			0.94 (0.72-1.23)	0.664
Unknown/Declined to state			0.51 (0.21-1.25)	0.143
Age at ED visit			1.00 (0.99-1.00)	0.198

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5,6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6,7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6,7, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	6,7,8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6,7,8, Table 2,3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Liver enzymes in the emergency department and subsequent heart failure diagnosis: A real-world analysis of practice patterns and diagnostic value

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Liver enzymes in the emergency department and subsequent heart failure diagnosis: A real-world analysis of practice patterns and diagnostic value

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Abstract:

Background Abnormal liver biochemical and function tests (LFTs) are associated with increased mortality in patients hospitalized with acute decompensated heart failure (ADHF). However, there are no specific guidelines to inform clinical practice related to LFTs in the diagnostic work up of ADHF in the ED. Whether LFTs are ordered in the ED in patients with suspected ADHF and what additional diagnostic information they provide is unclear.

Objectives To determine (1) if LFTs are ordered in the ED in patients with suspected ADHF and (2) if the pattern of LFT abnormalities are meaningfully associated with a discharge diagnosis of ADHF among patients for whom these tests were ordered

Design We conducted a single center retrospective cohort study of patients with suspected ADHF who were seen in the UCSF Medical Center emergency department using electronic medical records. We performed univariate and multivariate logistic regression to assess the association of LFT abnormalities with a final diagnosis of ADHF at hospital discharge. We studied the following LFTs: aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (alk phos) and total and direct bilirubin (TBili and DBili, respectively).

Participants All ED patients admitted with suspected ADHF from January 2017 to May 2018, defined as any patient who had a BNP ordered.

Results In 5,323 ED patients with suspected ADHF, 60% (n=3,184) had LFTs ordered; 34.6% were abnormal. Men comprised 56% of patients with abnormal LFTs and the average age was 67 years. The odds of a final diagnosis of ADHF in the univariate analysis was 59% higher in patients with abnormal LFTs (OR=1.59, [95% CI 1.35-1.87] p<0.001) and remained significant though attenuated after adjusting for BNP, race and ethnicity, and age (ORadj=1.31, [95% CI 1.09-1.57], p=0.004). Likelihood ratios (LRs) for abnormal and normal LFTs were 1.2 (95% CI: 1.21-1.28) and 0.76 (95% CI: 0.68-0.84), respectively.

Conclusions and Relevance A significant proportion (40%) of patients with suspected ADHF were missing LFTs in their ED workup. Among patients with LFTs, abnormal LFTs are associated with discharge diagnosis of ADHF after accounting for potential confounders, but their diagnostic value was relatively low. Future prospective studies are warranted to explore the role of LFTs in the workup of ADHF.

Strengths and Limitations of this study:

- Liver biochemical tests (LFTs) are commonly ordered in the emergency department; to our knowledge, this is the first study to evaluate the ordering behavior of providers in the ED in patients with suspected ADHF

- Guidelines suggest that LFT testing be considered in select cases, however, it is unclear what the utility of these tests are once they are ordered
- Although LFTs were associated with final diagnosis of ADHF, the diagnostic yield beyond biomarkers such as BNP was relatively low in this single center trial
- Our retrospective study does not evaluate the predictive value of LFTs in terms of outcomes such as all-cause mortality, but sets the framework for future investigation of this topic to avoid overuse of LFTs in ADHF in the ED

Introduction

Heart Failure (HF) is a leading cause of cardiovascular mortality, affecting 5.7 million Americans over the age of 20 from 2009-2012[1]. Projections show that the prevalence of HF will increase by 46% from 2012 to 2030[2,3]. Despite newer treatments, mortality remains high[4,5,6] and disproportionately affect African Americans[7,8].

Acute decompensated heart failure (ADHF) episodes lead to frequent emergency department (ED) visits among patients with HF. ADHF is defined as severe volume overload in the setting of poor cardiac output that is exacerbated by Additionally, readmission rates for ADHF are striking, with studies suggesting that 30-day and 180-day readmission rates approach 20-25% and 50%, respectively[9,10]. Although brain natriuretic peptide (BNP) has significantly improved the accuracy of ADHF diagnosis in the ED, patients are still misdiagnosed 10-20% of the time[11].

Liver function tests (LFTs) are commonly elevated in chronic heart failure[12] as a result of hemodynamic changes. However, LFTs have only more recently been studied as a predictor of heart failure prognosis during hospitalization for ADHF. The results of these studies have been

varied with respect to individual LFT parameters[13,14,15,16, 17,18, 19], but seem to suggest that elevated LFTs are associated with worse prognosis. All of these studies were conducted in patients with a confirmed diagnosis of ADHF, where baseline LFTs are obtained on admission. Although studies have explored LFT ordering patterns among ED providers,[20,21,22, 23,24]. LFTs have not specifically been examined in an ED population with suspected ADHF.

Heart failure is the most common and expensive reason for hospital admission for older Americans[25]. The American Heart Association's scientific statement on approaches to ADHF in the ED[26] recommends that LFTs should be considered in the work up of ADHF in select cases. The authors also emphasize that prior liver disease is an independent risk factor for worse mortality. However, surprisingly little research has been conducted in laboratory testing outside of routine BNP in patients with suspected ADHF in the ED and whether they offer additional diagnostic information. The lack of research in this area could lead to misuse of diagnostic tests, such as LFTs, and missed opportunities for early diagnosis in the ED.

Given the evidence for higher mortality in patients with ADHF and abnormal LFTs, it is necessary to assess if and how LFTs are utilized in the ED to inform the diagnosis of ADHF. Filling this gap in knowledge could potentially lead to an opportunity for earlier diagnosis, better resource utilization of laboratory testing and better risk stratification of ADHF. Using LFTs as an adjunct to BNP may also improve triaging of patients from the ED to appropriate levels of care. On the other hand, it is well known that overuse of tests in the ED does not improve outcomes[27]. In general, very little is understood about how ED providers use LFTs in their workup of ADHF in the first place, despite a large body of inpatient literature to suggest that abnormal LFTs can have prognostic value. This study aims to (1) evaluate the ordering patterns of LFTs in the ED in patients with suspected ADHF (2) in patients with LFTs, determine whether LFTs in an

abnormal range obtained in the ED are associated with a higher likelihood of subsequent discharge diagnosis of ADHF.

Methods

We retrospectively identified all unique patient encounters seen in the ED at UCSF Medical Center between January 2017 and May 2018, and identified patients admitted to the hospital with suspected ADHF, defined as patients who had a BNP drawn in the ED. Among those patients, we analyzed the association between LFT ordering behavior and results, and the outcome of ADHF, defined by final discharge diagnosis.

Lab Measurements:

We extracted all measurements of BNP, alanine aminotransaminase [ALT], aspartate aminotransaminase [AST], alkaline phosphatase [AlkPhos], total bilirubin [TBili] and direct bilirubin [DBili] from the electronic health record between January 2017 and May 2018. Each LFT measurement was categorized into ranges representing normal, mild-moderate elevation, and significant elevation (or missing completely). These ranges were ALT <34, =34-99, >100 mg/dL or missing, AST <34, =34-99, >100 mg/dL or missing, AlkPhos <123, =123-199, >200 mg/dL or missing, and TBili <1.2, =1.2-2.0, >2.0 mg/dL or missing, and DBili was defined as DBili <0.3, =0.3-2.0, >2.0 mg/dL or missing. We also looked at a global LFT measurement, defined as abnormal if any of the LFT measurements were abnormal per patient encounter (i.e., any LFT parameter fell into the mild-moderate or significantly elevated categories), missing if all LFT measurements were missing per patient encounter, or normal if all LFT measurements were normal per patient encounter. If patients had more than one LFT parameter measured per unique encounter, we selected the most elevated value per encounter for the analysis.

Other predictors

We examined other predictors including age at ED admission, race and ethnicity. Race and ethnicity were categorized as non-Hispanic Asian, non-Hispanic Black or African American, non-Hispanic white, non-Hispanic other identified race (which included Native American or other Pacific Islander, American Indian or Alaska Native, or patients who identified as "other race"), unknown or declined, or Hispanic, any race. BNP was categorized as high (>700 mg/dL), intermediate high (300-700 mg/dL), intermediate low (100-300 mg/dL), and low (<100 mg/dL).

Outcomes:

Because the diagnosis of ADHF is a clinical diagnosis[26], the final diagnosis given at discharge from the hospital was considered the "gold standard." We used any ADHF discharge diagnosis code (not just the first code) to define a final diagnosis of ADHF; see the Appendix for a listing of ICD-9 and ICD-10 codes we considered to indicate ADHF[27].

Statistical Analysis:

Baseline characteristics are presented as mean+/-SD for continuous variables and as frequencies and percentages for categorical variables. A p value of <0.05 was considered statistically significant and no adjustment was made for multiple comparisons. The data were analyzed with the use of commercially available statistical software (Stata, version 15).

To analyze the association between LFTs and ADHF, we first analyzed percentage of patients with an ADHF diagnosis according to categories of LFTs (and BNP) measurements. We used chi-square tests to evaluate these associations. We also calculated likelihood ratios (LRs) with 95% confidence intervals for each category of each predictor.

We then performed logistic regression to estimate the odds of final ADHF diagnosis for abnormal LFTs and each LFT parameter individually. We used normal LFTs as a reference point and included missing LFTs as a separate group from abnormal LFTs. We then adjusted analyses

for BNP, age at ED visit and race and ethnicity. We categorized BNP based on the *Breathing Not Properly* trial for the minimal cut off of BNP 100mg/dL. We further subdivided into high, intermediate high and intermediate low values of BNP to better assess granular changes in diagnostic accuracy of BNP as a covariate. Minimum values for LFTs were based on institution-specific cut offs for upper limit of normal, and further divided into intermediate values to capture granularity of the data. We felt this was important to distinguish given that hypoperfusion secondary to low cardiac output causing "shock liver" can cause extremely elevated LFTs whereas congestive hepatopathy causes mainly mildly elevated total bilirubin levels. We included past medical history which that would most commonly present with dyspnea as a chief complaint, such as COPD. We stratified other ED diagnoses to include diagnoses of any liver pathology to distinguish patients who might have had liver enzyme elevations from another cause, such as hepatic abscess or acute inflammation.

Patient and Public Involvement:

No patient involved.

Results

LFTs were ordered in 60% of patients admitted from the ED with suspected ADHF (n=5323). Baseline characteristics are presented in Table 1. We included past medical history that would be most likely to present with a chief complaint of dyspnea. Mean age was 71+/-16 years in patients with normal LFTs, 67+/-16 in patients with abnormal LFTs and 68+/-16 years in patients with missing LFTs. An ED diagnosis of ADHF for patients with normal, abnormal and missing LFTs was 8%, 15% and 13% of patients, respectively. At hospital discharge (obtained per patient encounter), 21% of patients with normal LFTs were diagnosed with ADHF, compared to 30% of patients with abnormal LFTs and 29% of patients with missing LFTs.

Prevalence of Liver Function Tests:

For patients with suspected ADHF in the ED, LFTs were obtained in 60% of patients; 25% had normal LFTs and 35% had abnormal LFTs (40% were missing). Figure 1 demonstrates LFT ordering behavior across BNP subgroups and final diagnosis of ADHF. The likelihood of final diagnosis of ADHF among patients with abnormal LFTs was 1.8% for patients with missing BNP, 3.6% for patients with BNP<100 mg/dL, 15% for patients with BNP 100-300 mg/dL, 37% for patients with BNP 300-700 mg/dL and 54% for patients with BNP >700mg/dL.

Likelihood Ratios (LRs):

Table 2 demonstrates positive and negative LRs for any abnormal LFT and individual LFT parameters. Positive and negative LRs for abnormal LFTs in patients with suspected ADHF were 1.20 and 0.76, respectively. The LRs were similar for ALT, AST, AlkPhos, TBili and DBili. The positive and negative LRs were stronger for BNP, with LR of 2.95, 1.42, 0.51 and 0.13 for BNP>700, 300-700, 100-300 and <100 mg/dL.

Univariate and Multivariate Logistic Regression:

Table 3 demonstrates final diagnosis of ADHF in patients with normal, abnormal and missing LFTs. In the univariate analysis, the odds of a final diagnosis of ADHF were 59% higher in patients with abnormal LFTs than those with normal LFTs (Odds ratio, OR 1.59 [95% Confidence Interval, 95% CI 1.35-1.87] p=0.000). After adjusting for age, race and ethnicity, and BNP, this association remained statistically significant (OR 1.31 [95% CI 1.09-1.57] p=0.004).

Individual LFT measurements were also associated with ADHF. For example, abnormal TBili was associated with higher odds (OR 1.41 [CI 1.26-1.62] p=0.000) after adjustment, and this was seen at both very high (TBili >2mg/dL) and slightly elevated (TBili =1.2-2 mg/dL). Missing TBili was also positively associated with the final diagnosis of ADHF (OR 1.39 [CI

1.19-1.61], p=0.000). Odds ratios for other individual LFT parameters can be found in the Appendix (Appendix Tables 1-5).

We also conducted an interaction analysis by race and ethnicity variables. No statistically significant interactions were detected.

Discussion

The diagnosis of ADHF in the ED is challenging. Dyspnea is one of the most common chief complaints assigned to a patient in the ED, however, there is no one piece of history, physical exam, electrocardiographic or radiographic finding to confirm the diagnosis before hospitalization[28]. Additionally, the final discharge diagnosis is discordant with the initial working diagnosis in the ED in almost 1 out of 4 cases[28]. Liver function tests are commonly found to be abnormal in patients with ADHF. Certain patterns, such as a small rise in total bilirubin or minimal elevations in intrahepatic enzymes, can suggest congestive hepatopathy. However, extreme elevations of intrahepatic enzymes often suggests shock liver in the setting of hypoperfusion in cardiogenic shock[16]. The aim of this study was to conduct a real-world analysis of the LFT ordering patterns of providers in the ED and to determine whether abnormal LFTs help to predict ADHF as a final outcome diagnosis. Our study revealed that LFTs are not ordered as part of the work up for a substantial proportion of patients with suspected ADHF in the ED (40%) . The odds of a final diagnosis of ADHF was positively associated with abnormal LFTs, and of the individual LFT measurements, TBili had the highest odds (OR 1.41). Positive LRs for abnormal LFTs, both composite and individual measurements, were in the range of 1.0-1.3 and thus unlikely to be of much value for diagnosis of ADHF. We did not detect interactions by demographically-defined subgroups.

In an in-depth analysis of LFTs in suspected ADHF in the ED, our study makes several important observations that can inform future practice. First, a significant number of patients with suspected ADHF had missing LFTs at this large tertiary center. A review[29] of the evaluation and management of ADHF in the ED indicates that testing should include liver function tests, as these tests are found to be abnormal in approximately 75% of patients and are associated with worse mortality. The authors conclude that in some ways, liver and renal function tests can be more helpful than even BNP, given their additional prognostic value. Even despite the AHA's scientific statement indicating that patients presenting with symptoms of ADHF should have LFTs considered, nearly 40% of patients in our study with suspected ADHF did not have LFTs ordered. Therefore, our study reveals a surprising and remarkable contrast to prior reviews and society guidelines. This could be for a number of reasons, including lack of prior liver disease in the medical history to prompt ED providers to obtain LFTs or that sufficient diagnostic information was obtained through clinical history, imaging or BNP alone. Regardless of the reason, our study importantly suggests that despite the association of abnormal LFTs to higher mortality in patients with ADHF, ED providers are not routinely ordering LFTs in this subset of patients.

Second, in our analysis of patients who had LFTs, we discovered a positive association between abnormal LFTs and the odds of final diagnosis of ADHF in patients with suspected ADHF. These results are comparable to several landmark heart failure trials which examine prognosis in ADHF. ASCEND-HF, the largest study to date to explore this question, evaluated the relationship of baseline LFTs to 30-day and 180-day mortality in patients admitted for ADHF. Similar to our study, only 59% of patients had baseline LFTs. Elevated TBili was associated with a 24% and 30% increase in 30-day and 180-day mortality, respectively[30]. The

authors found no association with AST or ALT. Another study found that abnormal ALT and AST values, as well as low albumin, have been associated with a combined endpoint of mortality or rehospitalization at 60 days[18]. Similarly, patients with ADHF had a high prevalence of abnormal LFTs at admission and was significantly associated with lower cardiac index and more elevated central venous pressures and MELD-XI scores[16]. However, both studies of baseline LFTs were inadequately powered to perform a multivariable analysis and did not account for other factors such as BNP. In the ED setting, making the diagnosis of ADHF is crucial to expediting treatment and thus reducing length of hospital stay and mortality[31].

Thus, to explore the true diagnostic value of these tests, we performed likelihood ratios which showed that the diagnostic value of these associations was relatively limited after adjustment for age, race and ethnicity, and BNP level, with LRs near 1.0. The LRs for BNP were strong: 2.95, 1.42, 0.51 and 0.13 for BNP>700, 300-700, 100-300 and <100 mg/dL. BNP and N-terminal pro-BNP have been shown to be effective in diagnosing ADHF because of their negative likelihood ratios, ranging from 0.1-0.14[28]. The LRs for BNP in our study were consistent with previous systematic reviews. To our knowledge, this is the first study to examine how LFTs predict ADHF in terms of LRs. The positive LR of 1.20 for abnormal LFTs and negative LR of 0.76 for normal LFTs that we found in our study are likely to have minimal diagnostic impact, especially when compared with the LRs for BNP.

In an era where value-based care is a major priority across hospital systems, it is important to critically assess the value of testing in the ED prior to admission. Studies such as the REDUCED trial[22] have examined the effects of uncoupling coagulation tests in the ED and found that implementing systemic changes to the order panel resulted in fewer tests ordered without a negative effect on patient outcomes. However, a clinical review[23] of the management

of elevated LFTs in the ED suggested that severely elevated LFTs suggest injury secondary to cardiorenal syndrome and should prompt physicians to evaluate for ADHF. Although we found that the diagnostic utility of abnormal LFTs was relatively low, a significant proportion of patients with suspected ADHF did not have LFTs ordered. This might have impacted the diagnostic value of abnormal LFT findings in the ED setting. The presence or absence of a lab test itself has been shown in prior studies to be predictive of survival. In an analysis of all tests ordered between 2005 and 2006 at two hospitals, researchers found that the presence of a lab test order itself was significantly associated with the odds of survival in more than 80% of lab tests, regardless of specific information related to the lab test itself[32]. This relates to our study in its key finding: the predictive value of healthcare process variables (guidelines, hospital metrics, the culture of how providers order tests at their institutions) might be more predictive of survival than the results of those tests themselves. We should undeniably strive to reduce unnecessary resource utilization in the ED. However, in ADHF, the high degree of mortality and costs related to advanced diagnostics such as echocardiogram renders further investigation of initial LFTs in the ED to inform guideline-directed practice. The use of LFTs in the ED for patients admitted with ADHF may serve as an important baseline for a patient's trajectory during their hospitalization. Given that abnormal LFTs are associated with worse mortality in ADHF during hospitalization, obtaining these tests prior to any intervention in the ED can further inform prognosis after receiving treatment. Prospective studies must be conducted to evaluate which patients would benefit from LFTs in terms of earlier diagnosis and risk stratification.

Our study has several limitations. First, this was a retrospective analysis of ED patients at a single site, which are susceptible to inherent limitations in data collection and study design. Additionally, our study used data from a single tertiary clinical medical center, which may not be generalizable to other emergency departments in other academic or community settings. We do

not have baseline LFTs for this group of patients, so it is possible that patients with chronic HF had preexisting abnormal LFTs. Additionally, we did not systematically obtain LFTs for all potentially eligible patients, and a substantial number of patients did not have LFTs obtained in the ED. Patients with missing LFTs had higher odds of final ADHF diagnosis at discharge, similar to patients with abnormal LFTs. A plausible explanation for this finding is that ED clinicians were less likely to order LFTs if they had a high degree of certainty that a patient was presenting with ADHF. This finding makes it difficult to interpret the outcome in patients with missing LFTs, because these patients potentially might have had abnormal LFTs if the tests were obtained. However, other studies, such as ADHERE-HF[33], had similar proportions of missing LFTs to our study. This finding in itself is interesting in that it suggests that providers may have been relying more heavily on other forms of diagnostic testing, such as echocardiogram, when LFTs might have given a more cost effective insight into volume status or effective circulating volume. An important study done by Vyskocilova et al examined a large repository of patients with ADHF across 9 university hospitals and 5 regional health care facilities in the Czech Republic. They found that abnormal LFTs were found in 76% of patients with ADHF and patients with cardiogenic shock were more likely to have abnormal LFTs than those with mild ADHF or pulmonary edema[34]. They found that abnormal LFTs were highly suggestive of more severe ADHF and reflected worse NYHA class. They argued that it is crucial to assess LFTs in the initial diagnostic investigation of ADHF as it informs management and stratifies patients based on severity. Although patients with missing LFTs were similarly diagnosed with ADHF to those with abnormal LFTs, it is possible that LFTs performed in the ED would have facilitated any additional work up performed after admission.

On the other hand, our study has important strengths, especially in contrast to prior analyses. First, we studied a large sample of patients seen in the ED prior to admission, where an initial suspicion for ADHF is most crucial to guide early evidence-based diagnosis and management. Second, our study was powered to adjust for BNP, which is known to be a strong predictor of ADHF. Third, our study estimated LRs, a key step in translating diagnostic test findings to clinical practice.

Our real-world analysis of patients admitted from the ED with suspected ADHF found that LFTs were not ordered for 40% of patients. Among patients who had LFTs ordered, abnormal LFTs in the ED are associated with a final ADHF diagnosis, the LRs indicate their limited diagnostic value, particularly in contrast with BNP. To balance the risks of overuse of tests and high inpatient mortality associated with abnormal LFTs, it is imperative to prospectively evaluate LFTs in the workup of ADHF and incorporate recommendations in society guidelines for clinical practice.

Statements:
There was no funding for this work. None of the authors have competing interests. No data are available. Data were de-identified so Research Ethics Approval was not required for this study.

Author Contributions:
Each author contributed equally to the planning, conduct and reporting of the work described in the manuscript.
Concept, design, analysis of the data, interpretation of the data, and writing of the manuscript draft were performed by EV
Design, analysis, interpretation of the data, and writing/extensive editing of the manuscript were performed by MJP
Interpretation of the data and writing/extensive editing of the manuscript were performed by JAT
Provision of the data, writing/extensive editing of the manuscript were performed by AH

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Table 1. Baseline Characteristics of Patients with Suspected ADHF in the Emergency Department

Characteristic	LFTs – Normal Range N=1,342	LFTs - Abnormal Range N=1,842	LFTs – Missing N=2,139	P value[a]
Age at ED visit – mean in years+/-SD	71 +/-16	67 +/-16	68 +/-16	<0.001
Sex Identified – No.(%)				
Male	633 (47%)	1,036 (56%)	1,113 (53%)	<0.001
Female	709 (53%)	806 (44%)	1,026 (48%)	
Race and Ethnicity – No.(%)				
Non-Hispanic Asian	303 (23%)	459 (25%)	442 (21%)	<0.001
Non-Hispanic Black or African American	236 (18%)	375 (20%)	401 (19%)	
Non-Hispanic White	546 (41%)	658 (36%)	918 (43%)	
Hispanic, any race	134 (10%)	202 (11%)	181 (9%)	
Other	108 (8%)	132 (7%)	174 (8%)	
Unknown/Declined to state	15 (1%)	16 (1%)	20 (1%)	
Insurance[b] No.(%)				
Private	147 (11%)	274 (13%)	295 (14%)	<0.001
MediCal	218 (16%)	382 (21%)	367 (17%)	
Medicare	927 (69%)	1,086 (59%)	1,357 (64%)	
Other	49 (4%)	23 (1.3%)	117 (5%)	
Diuretics in the ED?				
Yes	250 (19%)	449 (24%)	483 (23%)	0.001
No	1,092 (81%)	1,393 (76%)	1,656 (77%)	
BNP* in the ED?				
High BNP (>700mg/dL)	308 (23%)	636 (35%)	618 (29%)	<0.001
Intermediate High BNP(300-700mg/dL)	278 (21%)	357 (19%)	441 (21%)	
Intermediate Low BNP(100-300 mg/dL)	339 (25%)	376 (20%)	455 (21%)	
Low BNP (<100 mg/dL)	417 (31%)	473 (26%)	625 (29%)	
Past Medical History				
History of Asthma	251 (19%)	244 (13%)	379 (18%)	<0.001
History of COPD	345 (26%)	412 (22%)	580 (27%)	0.002
History of Smoking	699 (52%)	928 (50%)	1,129 (53%)	0.012

ED Diagnosis**				
ADHF†	107 (8%)	274 (15%)	281 (13%)	<0.001
Pneumonia	175 (13%)	243 (13%)	330 (15%)	0.025
COPD exacerbation	124 (9%)	96 (5%)	235 (11%)	<0.001
Asthma exacerbation	27 (2%)	28 (2%)	68 (3%)	0.001
Acute Upper Respiratory Infection	2 (0.2%)	1 (0.1%)	8 (0.4%)	0.028
Any Liver Pathology‡	12 (1%)	107 (6%)	16 (1%)	<0.001
Final Discharge Diagnosis°				
ADHF	283 (21%)	549 (30%)	622 (29%)	<0.001
Not ADHF	1,059 (79%)	1,293 (70%)	1,517 (71%)	

[a]P values based on Chi Square analysis for categorical variables and ANOVA for continuous variables
[b]Insurance is categorized as "Private" (Aetna, Blue Cross, Blue Shield, GCSS/GHP, Capitation, Charity, Commercial, Covered California, Covered California – MediCal, HealthNet, Institutional, and Kaiser), "MediCal" (Medicaid/MIA/CMSP, MediCal managed care, MediCal pending, MediCal standard) "Medicare" (Medicare, Medicare Advantage HMO/Senior, Medicare Advantage PFFS) and "Other" (Self-pay, United Health Care, Worker's compensation)
*BNP=Brain Natriuretic Peptide
**ED Diagnosis was obtained through specification of ICD10 codes for respiratory diagnoses and liver-related diseases
†ADHF=Acute Decompensated Heart Failure
‡Any liver pathology includes ICD10 codes for the following: alcoholic liver disease, toxic liver disease, hepatic failure (not elsewhere specified), chronic hepatitis (not elsewhere specified), fibrosis and cirrhosis of liver, other inflammatory liver diseases, other diseases of the liver, liver disorders in diseases of the liver (classified elsewhere)
¶Suspected ADHF is defined as patients who had a BNP ordered in the ED
°Final discharge diagnosis of ADHF is based on ICD 10 codes for a diagnosis of heart failure named on the discharge summary for a patient's specific encounter

Table 2. Liver Function Tests, BNP and Acute Decompensated Heart Failure at Discharge in ED patients with suspected ADHF (n=5,323)

Characteristic	N	% with ADHF diagnosis at discharge	p-value*	LR(95% CI)
Liver Function Tests (LFTs)				
Abnormal LFTs	1,842	30%	0.000	1.20 (1.13-1.28)
Normal LFTs	1342	21%		0.76 (0.68-0.84)
Missing LFTs	2139	29%		-
Alanine Transaminase (ALT)				
ALT >=100 mg/dL	168	27%	0.017	1.03 (0.74-1.44)
ALT 34-99 mg/dL	684	30%		1.19 (1.03-1.37)
ALT <34 mg/dL	2,310	25%		0.95 (0.90-1.00)
Missing ALT	2,161	29%		-
Aspartate Transaminase (AST)				
AST>=100 mg/dL	246	24%	0.000	0.87 (0.66-1.16)
AST 34-99 mg/dL	1,070	30%		1.22 (1.10-1.35)
AST <34 mg/dL	1,864	24%		0.90 (0.84-0.97)
Missing AST	2,143	29%		-
Alkaline Phosphate (AlkPhos)				
AlkPhos >=200 mg/dL	249	22%	0.004	0.81 (0.60-1.08)
AlkPhos 123-199 mg/dL	420	31%		1.26 (1.04-1.53)
AlkPhos <123 mg/dL	2,451	26%		0.98 (0.94-1.02)
Missing AlkPhos	2,203	29%		-
Total Bilirubin				
Total Bilirubin>2mg/dL	323	32%	0.000	1.32 (1.06-1.65)
Total Bilirubin 1.2-2 mg/dL	501	36%		1.59 (1.35-1.88)
Total Bilirubin<1.2 mg/dL	2,314	23%		0.85 (0.81-0.90)
Missing Total Bilirubin	2,185	29%		-
Direct Bilirubin				
Direct Bilirubin>2 mg/dL	18	22%	0.007	0.62 (0.22-1.75)

Direct Bilirubin 0.3-2 mg/dL	48	48%		1.99 (1.32-3.00)
Direct Bilirubin<0.3 mg/dL	51	20%		0.53 (0.30-0.93)
Missing Direct Bilirubin	5,206	27%		-
BNP**				
High BNP (>700mg/dL)	1,562	53%	0.000	2.95(2.72-3.19)
Intermediate High BNP(300-700mg/dL)	1,076	35%		1.42(1.28-1.59)
Intermediate Low BNP(100-300 mg/dL)	1,170	16%		0.51(0.44-0.59)
Low BNP (<100 mg/dL)	1,515	5%		0.13(0.10-0.17)

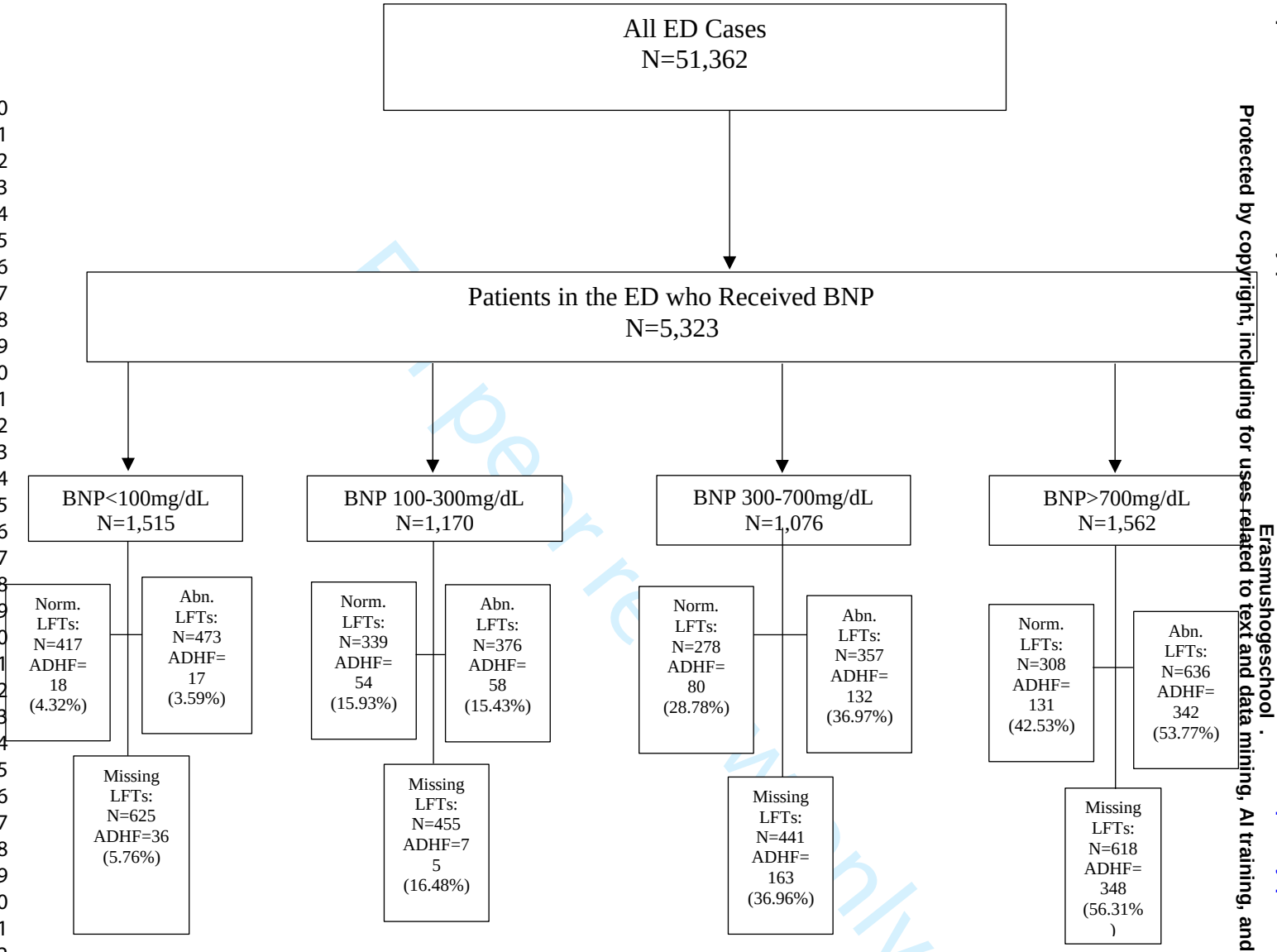
*P-values are based on Chi-Square test
**BNP=Brain Natriuretic Peptide

Table 3. Univariate and Multivariate Logistic Regression Analysis of High LFTs and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5,323)

Characteristic	Univariate Analysis		Multivariate Analysis*	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Abnormal LFTs	1.59(1.35-1.87)	0.000	1.29 (1.08-1.55)	0.006
Missing LFTs	1.53(1.31-1.80)	0.000	1.42 (1.19-1.71)	0.000
Normal LFTs	Reference	Reference	Reference	Reference
BNP**				
High BNP (>700mg/dL)	22.53(17.41-29.17)	0.000	22.53 (17.35-29.28)	0.000
Intermediate High BNP(300-700mg/dL)	10.88(8.31-14.24)	0.000	11.10 (8.45-14.60)	0.000
Intermediate Low BNP (100-300 mg/dL)	3.87(2.91-5.14)	0.000	4.00 (3.00-5.33)	0.000
Low BNP(100 mg/dL)	Reference	Reference	Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65-1.01)	0.062
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.12)	0.438
Other, Non-Hispanic			1.06 (0.80-1.41)	0.695
Hispanic, any race			0.97 (0.74-1.26)	0.809
Unknown/Declined to state			0.52 (0.21-1.25)	0.144
Age at ED visit, per year			1.00 (0.99-1.00)	0.395
Male sex			1.21(1.06-1.39)	0.006

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity
**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit
†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Figure 1. Classification Tree



Appendix:

Appendix Table 1. Univariate and Multivariate Logistic Regression Analysis of High ALT and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
ALT>100 mg/dL	1.09(0.76-1.55)	0.638	1.01 (0.68-1.50)	0.966
ALT 34-99 mg/dL	1.26(1.04-1.52)	0.018	1.22 (0.98-1.50)	0.072
ALT<34 mg/dL	Reference	Reference	Reference	Reference
Missing ALT	1.21 (1.06-1.38)	0.005	1.26 (1.08 -1.46)	0.002
High BNP (>700mg/dL)			22.96 (17.68-29.82)	0.000
Intermediate High BNP(300-700mg/dL)			11.21 (8.53-14.73)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.02 (3.02-5.36)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65-1.01)	0.064
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.92 (0.76-1.12)	0.422
Other, Non-Hispanic			1.03 (0.77-1.37)	0.846
Hispanic, any race			0.97 (0.74-1.26)	0.807
Unknown/Declined to state			0.50 (0.21-1.23)	0.132
Age at ED visit			1.00 (0.99-1.00)	0.201
Male Sex			1.21(1.06-1.39)	0.005

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 2. Univariate and Multivariate Logistic Regression Analysis of High AST and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
AST>100 mg/dL	0.97 (0.71-1.32)	0.831	1.02 (0.71-1.43)	0.961
AST 34-99 mg/dL	1.35 (1.15-1.60)	0.000	1.15 (0.95 -1.39)	0.144
AST<34 mg/dL	Reference	Reference	Reference	Reference
Missing AST	1.28 (1.11-1.48)	0.001	1.28 (1.09-1.50)	0.002
High BNP (>700mg/dL)			22.82 (17.56 - 29.63)	0.000
Intermediate High BNP(300-700mg/dL)			11.17 (8.50-14.67)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.01 (3.01-5.35)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.82 (0.66-1.02)	0.069
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.13)	0.453
Other, Non-Hispanic			1.04 (0.80-1.41)	0.810
Hispanic, any race			0.97 (0.75-1.27)	0.842
Unknown/Declined to state			0.51 (0.21-1.25)	0.140
Age at ED visit			1.00 (0.99-1.00)	0.295
Male Sex			1.22(1.06-1.40)	0.004

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 3. Univariate and Multivariate Logistic Regression Analysis of High AlkPhos and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)*

Characteristic	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
AlkPhos>200 mg/dL	0.82(0.60-1.13)	0.222	0.80 (0.56-1.12)	0.201
AlkPhos 123-199 mg/dL	1.29(1.03-1.61)	0.029	1.03 (0.56-1.13)	0.801
AlkPhos<123 mg/dL	Reference	Reference	Reference	Reference
Missing AlkPhos	1.19(1.05-1.36)	0.007	1.21 (1.05-1.40)	0.009
BNP**				
High BNP (>700mg/dL)			22.97 (17.68-29.84)	0.000
Intermediate High BNP(300-700mg/dL)			11.16 (8.49-14.67)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.00 (3.00-5.33)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.82 (0.66 -1.02)	0.077
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.14)	0.439
Other, Non-Hispanic			1.03 (0.78 -1.38)	0.819
Hispanic, any race			0.98 (0.75-1.27)	0.868
Unknown/Declined to state			0.51 (0.21 -1.25)	0.142
Age at ED visit			1.00 (0.99-1.00)	0.246
Male Sex			1.22(1.07-1.40)	0.004

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 4. Univariate and Multivariate Logistic Regression Analysis of High DBili and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
DBili>2 mg/dL	1.17(0.32-4.34)	0.813	1.37 (0.33-5.67)	0.667
DBili 0.3-2 mg/dL	3.77(1.54-9.22)	0.004	3.63 (1.32-10.03)	0.013
DBili<0.3 mg/dL	Reference	Reference	Reference	Reference
Missing DBili	1.53(0.77-3.07)	0.227	1.45 (0.68-3.10)	0.341
BNP**				
High BNP (>700mg/dL)			22.86 (17.60 - 29.69)	0.000
Intermediate High BNP(300-700mg/dL)			11.17 (8.50 - 14.68)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.01 (3.01-5.35)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65 -1.01)	0.062
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.12)	0.450
Other, Non-Hispanic			1.03 (0.77-1.37)	0.838
Hispanic, any race			0.95 (0.74-1.25)	0.759
Unknown/Declined to state			0.50 (0.21-1.23)	0.131
Age at ED visit			1.00 (0.99-1.00)	0.298
Male Sex			1.22(1.07-1.40)	0.004

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 5. Univariate and Multivariate Logistic Regression Analysis of High LFTs and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5,323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
TBili>2 mg/dL	1.55 (1.20-2.00)	0.001	1.36 (1.10-1.75)	0.036
TBili 1.2-2 mg/dL	1.87 (1.52-2.30)	0.000	1.39 (1.02-1.82)	0.005
TBili<1.2 mg/dL	Reference	Reference	Reference	Reference
Missing TBili	1.40 (1.22-1.60)	0.000	1.38 (1.19-1.60)	0.000
BNP				
High BNP (>700mg/dL)			22.51 (17.32 - 29.44)	0.000
Intermediate High BNP(300-700mg/dL)			11.13 (8.46 - 14.64)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.00 (3.00-5.33)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65 -1.01)	0.061
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.92 (0.76-1.11)	0.373
Other, Non-Hispanic			1.03 (0.78-1.37)	0.827
Hispanic, any race			0.95 (0.73-1.24)	0.732
Unknown/Declined to state			0.50 (0.21-1.22)	0.129
Age at ED visit			1.00 (0.99-1.00)	0.198
Male Sex			1.21(1.05-1.38)	0.007

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5,6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6,7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6,7, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	6,7,8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6,7,8, Table 2,3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Use and diagnostic value of liver enzyme tests in the emergency department and subsequent heart failure diagnosis: a retrospective cohort study

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Use and diagnostic value of liver enzyme tests in the emergency department and subsequent heart failure diagnosis: a retrospective cohort study

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Abstract:

Objectives To determine (1) if LFTs are ordered in the ED in patients with suspected ADHF and (2) if the pattern of LFT abnormalities are meaningfully associated with a discharge diagnosis of ADHF among patients for whom these tests were ordered.

Setting We conducted a single-center retrospective cohort study of patients with suspected ADHF who were seen in an academic tertiary emergency department using electronic medical records.

Participants All ED patients admitted with suspected ADHF from January 2017 to May 2018, defined as any patient who had a BNP ordered.

Primary outcome The primary outcome was ADHF diagnosis at discharge.

Results In 5,323 ED patients with suspected ADHF, 60% (n=3,184) had LFTs ordered; 34.6% were abnormal. Men comprised 56% of patients with abnormal LFTs and the average age was 67 years. The odds of a final diagnosis of ADHF in the univariate analysis was 59% higher in patients with abnormal LFTs (OR=1.59, [95% CI 1.35-1.87] p<0.001) and remained significant though attenuated after adjusting for BNP, race and ethnicity, and age (ORadj=1.31, [95% CI 1.09-1.57], p=0.004). Likelihood ratios (LRs) for abnormal and normal LFTs were 1.2 (95% CI: 1.21-1.28) and 0.76 (95% CI: 0.68-0.84), respectively.

Conclusions A significant proportion (40%) of patients with suspected ADHF were missing LFTs in their ED workup. Among patients with LFTs, abnormal LFTs are associated with discharge diagnosis of ADHF after accounting for potential confounders, but their diagnostic value was relatively low. Future prospective studies are warranted to explore the role of LFTs in the workup of ADHF.

Strengths and limitations of this study

- Liver biochemical tests (LFTs) are commonly ordered in the emergency department; to our knowledge, this is the first study to evaluate the ordering behavior of providers in the ED in patients with suspected ADHF.
- The retrospective nature of our study permitted a cost-effective, efficient means of evaluating a major clinical query in a real world setting to inform management of ED patients.
- This cohort analysis allowed for the inclusion of a large number of patients for increased generalizability.
- All retrospective study designs are subject to possible selection biases related to missing data.

- Our retrospective study does not evaluate the predictive value of LFTs in terms of outcomes such as all-cause mortality, but sets the framework for future investigation of this topic to avoid overuse of LFTs in ADHF in the ED.

Introduction

Heart Failure (HF) is a leading cause of cardiovascular mortality, affecting 5.7 million Americans over the age of 20 from 2009-2012[1]. Projections show that the prevalence of HF will increase by 46% from 2012 to 2030[2,3]. Despite newer treatments, mortality remains high[4,5,6] and disproportionately affect African Americans[7,8].

Acute decompensated heart failure (ADHF) episodes lead to frequent emergency department (ED) visits among patients with HF. ADHF is defined as severe volume overload in the setting of poor cardiac output that is exacerbated by Additionally, readmission rates for ADHF are striking, with studies suggesting that 30-day and 180-day readmission rates approach 20-25% and 50%, respectively[9,10]. Although brain natriuretic peptide (BNP) has significantly improved the accuracy of ADHF diagnosis in the ED, patients are still misdiagnosed 10-20% of the time[11].

Liver function tests (LFTs) are commonly elevated in chronic heart failure[12] as a result of hemodynamic changes. However, LFTs have only more recently been studied as a predictor of heart failure prognosis during hospitalization for ADHF. The results of these studies have been varied with respect to individual LFT parameters[13,14,15,16, 17,18, 19], but seem to suggest that elevated LFTs are associated with worse prognosis. All of these studies were conducted in patients with a confirmed diagnosis of ADHF, where baseline LFTs are obtained on admission.

Although studies have explored LFT ordering patterns among ED providers,[20,21,22, 23,24]. LFTs have not specifically been examined in an ED population with suspected ADHF.

Heart failure is the most common and expensive reason for hospital admission for older Americans[25]. The American Heart Association's scientific statement on approaches to ADHF in the ED[26] recommends that LFTs should be considered in the work up of ADHF in select cases. The authors also emphasize that prior liver disease is an independent risk factor for worse mortality. However, surprisingly little research has been conducted in laboratory testing outside of routine BNP in patients with suspected ADHF in the ED and whether they offer additional diagnostic information. The lack of research in this area could lead to misuse of diagnostic tests, such as LFTs, and missed opportunities for early diagnosis in the ED.

Given the evidence for higher mortality in patients with ADHF and abnormal LFTs, it is necessary to assess if and how LFTs are utilized in the ED to inform the diagnosis of ADHF. Filling this gap in knowledge could potentially lead to an opportunity for earlier diagnosis, better resource utilization of laboratory testing and better risk stratification of ADHF. Using LFTs as an adjunct to BNP may also improve triaging of patients from the ED to appropriate levels of care. On the other hand, it is well known that overuse of tests in the ED does not improve outcomes[27]. In general, very little is understood about how ED providers use LFTs in their workup of ADHF in the first place, despite a large body of inpatient literature to suggest that abnormal LFTs can have prognostic value. This study aims to (1) evaluate the ordering patterns of LFTs in the ED in patients with suspected ADHF (2) in patients with LFTs, determine whether LFTs in an abnormal range obtained in the ED are associated with a higher likelihood of subsequent discharge diagnosis of ADHF.

Methods

We retrospectively identified all unique patient encounters seen in the ED at UCSF Medical Center between January 2017 and May 2018, and identified patients admitted to the hospital with suspected ADHF, defined as patients who had a BNP drawn in the ED. Among those patients, we analyzed the association between LFT ordering behavior and results, and the outcome of ADHF, defined by final discharge diagnosis.

Laboratory measurements

We extracted all measurements of BNP, alanine aminotransaminase [ALT], aspartate aminotransaminase [AST], alkaline phosphatase [AlkPhos], total bilirubin [TBili] and direct bilirubin [DBili] from the electronic health record between January 2017 and May 2018. Each LFT measurement was categorized into ranges representing normal, mild-moderate elevation, and significant elevation (or missing completely). These ranges were ALT <34, =34-99, >100 mg/dL or missing, AST <34, =34-99, >100 mg/dL or missing, AlkPhos <123, =123-199, >200 mg/dL or missing, and TBili <1.2, =1.2-2.0, >2.0 mg/dL or missing, and DBili was defined as DBili <0.3, =0.3-2.0, >2.0 mg/dL or missing. We also looked at a global LFT measurement, defined as abnormal if any of the LFT measurements were abnormal per patient encounter (i.e., any LFT parameter fell into the mild-moderate or significantly elevated categories), missing if all LFT measurements were missing per patient encounter, or normal if all LFT measurements were normal per patient encounter. If patients had more than one LFT parameter measured per unique encounter, we selected the most elevated value per encounter for the analysis.

Other predictors

We examined other predictors including age at ED admission, race and ethnicity. Race and ethnicity were categorized as non-Hispanic Asian, non-Hispanic Black or African American, non-Hispanic white, non-Hispanic other identified race (which included Native American or

other Pacific Islander, American Indian or Alaska Native, or patients who identified as "other race"), unknown or declined, or Hispanic, any race. BNP was categorized as high (>700 mg/dL), intermediate high (300-700 mg/dL), intermediate low (100-300 mg/dL), and low (<100 mg/dL).

Outcomes

Because the diagnosis of ADHF is a clinical diagnosis[26], the final diagnosis given at discharge from the hospital was considered the "gold standard." We used any ADHF discharge diagnosis code (not just the first code) to define a final diagnosis of ADHF; see the Appendix for a listing of ICD-9 and ICD-10 codes we considered to indicate ADHF[27].

Statistical analysis

Baseline characteristics are presented as mean+/-SD for continuous variables and as frequencies and percentages for categorical variables. A p value of <0.05 was considered statistically significant and no adjustment was made for multiple comparisons. The data were analyzed with the use of commercially available statistical software (Stata, version 15).

To analyze the association between LFTs and ADHF, we first analyzed percentage of patients with an ADHF diagnosis according to categories of LFTs (and BNP) measurements. We used chi-square tests to evaluate these associations. We also calculated likelihood ratios (LRs) with 95% confidence intervals for each category of each predictor.

We then performed logistic regression to estimate the odds of final ADHF diagnosis for abnormal LFTs and each LFT parameter individually. We used normal LFTs as a reference point and included missing LFTs as a separate group from abnormal LFTs. We then adjusted analyses for BNP, age at ED visit and race and ethnicity. We categorized BNP based on the *Breathing Not Properly* trial for the minimal cut off of BNP 100mg/dL. We further subdivided into high, intermediate high and intermediate low values of BNP to better assess granular changes in

diagnostic accuracy of BNP as a covariate. Minimum values for LFTs were based on institution-specific cut offs for upper limit of normal, and further divided into intermediate values to capture granularity of the data. We felt this was important to distinguish given that hypoperfusion secondary to low cardiac output causing "shock liver" can cause extremely elevated LFTs whereas congestive hepatopathy causes mainly mildly elevated total bilirubin levels. We included past medical history which that would most commonly present with dyspnea as a chief complaint, such as COPD. We stratified other ED diagnoses to include diagnoses of any liver pathology to distinguish patients who might have had liver enzyme elevations from another cause, such as hepatic abscess or acute inflammation. The authors (MJP and EV) were responsible for all data cleaning, which was performed exclusively through Stata on the UCSF encrypted desktop.

Patient and Public Involvement

No patient involved.

Results

LFTs were ordered in 60% of patients admitted from the ED with suspected ADHF (n=5323). Baseline characteristics are presented in Table 1. We included past medical history that would be most likely to present with a chief complaint of dyspnea. Mean age was 71+/-16 years in patients with normal LFTs, 67+/-16 in patients with abnormal LFTs and 68+/-16 years in patients with missing LFTs. An ED diagnosis of ADHF for patients with normal, abnormal and missing LFTs was 8%, 15% and 13% of patients, respectively. At hospital discharge (obtained per patient encounter), 21% of patients with normal LFTs were diagnosed with ADHF, compared to 30% of patients with abnormal LFTs and 29% of patients with missing LFTs.

Prevalence of liver function tests

For patients with suspected ADHF in the ED, LFTs were obtained in 60% of patients; 25% had normal LFTs and 35% had abnormal LFTs (40% were missing). Figure 1 demonstrates LFT ordering behavior across BNP subgroups and final diagnosis of ADHF. The likelihood of final diagnosis of ADHF among patients with abnormal LFTs was 1.8% for patients with missing BNP, 3.6% for patients with BNP<100 mg/dL, 15% for patients with BNP 100-300 mg/dL, 37% for patients with BNP 300-700 mg/dL and 54% for patients with BNP >700mg/dL.

Likelihood ratios (LRs)

Table 2 demonstrates positive and negative LRs for any abnormal LFT and individual LFT parameters. Positive and negative LRs for abnormal LFTs in patients with suspected ADHF were 1.20 and 0.76, respectively. The LRs were similar for ALT, AST, AlkPhos, TBili and DBili. The positive and negative LRs were stronger for BNP, with LR of 2.95, 1.42, 0.51 and 0.13 for BNP>700, 300-700, 100-300 and <100 mg/dL.

Univariate and multivariate logistic regression

Table 3 demonstrates final diagnosis of ADHF in patients with normal, abnormal and missing LFTs. In the univariate analysis, the odds of a final diagnosis of ADHF were 59% higher in patients with abnormal LFTs than those with normal LFTs (Odds ratio, OR 1.59 [95% Confidence Interval, 95% CI 1.35-1.87] p=0.000). After adjusting for age, race and ethnicity, and BNP, this association remained statistically significant (OR 1.31 [95% CI 1.09-1.57] p=0.004).

Individual LFT measurements were also associated with ADHF. For example, abnormal TBili was associated with higher odds (OR 1.41 [CI 1.26-1.62] p=0.000) after adjustment, and this was seen at both very high (TBili >2mg/dL) and slightly elevated (TBili =1.2-2 mg/dL). Missing TBili was also positively associated with the final diagnosis of ADHF (OR 1.39 [CI

1.19-1.61], p=0.000). Odds ratios for other individual LFT parameters can be found in the Appendix (See Appendix Tables 1-5).

We also conducted an interaction analysis by race and ethnicity variables. No statistically significant interactions were detected.

Discussion

The diagnosis of ADHF in the ED is challenging. Dyspnea is one of the most common chief complaints assigned to a patient in the ED, however, there is no one piece of history, physical exam, electrocardiographic or radiographic finding to confirm the diagnosis before hospitalization[28]. Additionally, the final discharge diagnosis is discordant with the initial working diagnosis in the ED in almost 1 out of 4 cases[28]. Liver function tests are commonly found to be abnormal in patients with ADHF. Certain patterns, such as a small rise in total bilirubin or minimal elevations in intrahepatic enzymes, can suggest congestive hepatopathy. However, extreme elevations of intrahepatic enzymes often suggests shock liver in the setting of hypoperfusion in cardiogenic shock[16]. The aim of this study was to conduct a real-world analysis of the LFT ordering patterns of providers in the ED and to determine whether abnormal LFTs help to predict ADHF as a final outcome diagnosis. Our study revealed that LFTs are not ordered as part of the work up for a substantial proportion of patients with suspected ADHF in the ED (40%) . The odds of a final diagnosis of ADHF was positively associated with abnormal LFTs, and of the individual LFT measurements, TBili had the highest odds (OR 1.41). Positive LRs for abnormal LFTs, both composite and individual measurements, were in the range of 1.0-1.3 and thus unlikely to be of much value for diagnosis of ADHF. We did not detect interactions by demographically-defined subgroups.

In an in-depth analysis of LFTs in suspected ADHF in the ED, our study makes several important observations that can inform future practice. First, a significant number of patients with suspected ADHF had missing LFTs at this large tertiary center. A review[29] of the evaluation and management of ADHF in the ED indicates that testing should include liver function tests, as these tests are found to be abnormal in approximately 75% of patients and are associated with worse mortality. The authors conclude that in some ways, liver and renal function tests can be more helpful than even BNP, given their additional prognostic value. Even despite the AHA's scientific statement indicating that patients presenting with symptoms of ADHF should have LFTs considered, nearly 40% of patients in our study with suspected ADHF did not have LFTs ordered. Therefore, our study reveals a surprising and remarkable contrast to prior reviews and society guidelines. This could be for a number of reasons, including lack of prior liver disease in the medical history to prompt ED providers to obtain LFTs or that sufficient diagnostic information was obtained through clinical history, imaging or BNP alone. Regardless of the reason, our study importantly suggests that despite the association of abnormal LFTs to higher mortality in patients with ADHF, ED providers are not routinely ordering LFTs in this subset of patients.

Second, in our analysis of patients who had LFTs, we discovered a positive association between abnormal LFTs and the odds of final diagnosis of ADHF in patients with suspected ADHF. These results are comparable to several landmark heart failure trials which examine prognosis in ADHF. ASCEND-HF, the largest study to date to explore this question, evaluated the relationship of baseline LFTs to 30-day and 180-day mortality in patients admitted for ADHF. Similar to our study, only 59% of patients had baseline LFTs. Elevated TBili was associated with a 24% and 30% increase in 30-day and 180-day mortality, respectively[30]. The

authors found no association with AST or ALT. Another study found that abnormal ALT and AST values, as well as low albumin, have been associated with a combined endpoint of mortality or rehospitalization at 60 days[18]. Similarly, patients with ADHF had a high prevalence of abnormal LFTs at admission and was significantly associated with lower cardiac index and more elevated central venous pressures and MELD-XI scores[16]. However, both studies of baseline LFTs were inadequately powered to perform a multivariable analysis and did not account for other factors such as BNP. In the ED setting, making the diagnosis of ADHF is crucial to expediting treatment and thus reducing length of hospital stay and mortality[31].

Thus, to explore the true diagnostic value of these tests, we performed likelihood ratios which showed that the diagnostic value of these associations was relatively limited after adjustment for age, race and ethnicity, and BNP level, with LRs near 1.0. The LRs for BNP were strong: 2.95, 1.42, 0.51 and 0.13 for BNP>700, 300-700, 100-300 and <100 mg/dL. BNP and N-terminal pro-BNP have been shown to be effective in diagnosing ADHF because of their negative likelihood ratios, ranging from 0.1-0.14[28]. The LRs for BNP in our study were consistent with previous systematic reviews. To our knowledge, this is the first study to examine how LFTs predict ADHF in terms of LRs. The positive LR of 1.20 for abnormal LFTs and negative LR of 0.76 for normal LFTs that we found in our study are likely to have minimal diagnostic impact, especially when compared with the LRs for BNP.

In an era where value-based care is a major priority across hospital systems, it is important to critically assess the value of testing in the ED prior to admission. Studies such as the REDUCED trial[22] have examined the effects of uncoupling coagulation tests in the ED and found that implementing systemic changes to the order panel resulted in fewer tests ordered without a negative effect on patient outcomes. However, a clinical review[23] of the management

of elevated LFTs in the ED suggested that severely elevated LFTs suggest injury secondary to cardiorenal syndrome and should prompt physicians to evaluate for ADHF. Although we found that the diagnostic utility of abnormal LFTs was relatively low, a significant proportion of patients with suspected ADHF did not have LFTs ordered. This might have impacted the diagnostic value of abnormal LFT findings in the ED setting. The presence or absence of a lab test itself has been shown in prior studies to be predictive of survival. In an analysis of all tests ordered between 2005 and 2006 at two hospitals, researchers found that the presence of a lab test order itself was significantly associated with the odds of survival in more than 80% of lab tests, regardless of specific information related to the lab test itself[32]. This relates to our study in its key finding: the predictive value of healthcare process variables (guidelines, hospital metrics, the culture of how providers order tests at their institutions) might be more predictive of survival than the results of those tests themselves. We should undeniably strive to reduce unnecessary resource utilization in the ED. However, in ADHF, the high degree of mortality and costs related to advanced diagnostics such as echocardiogram renders further investigation of initial LFTs in the ED to inform guideline-directed practice. The use of LFTs in the ED for patients admitted with ADHF may serve as an important baseline for a patient's trajectory during their hospitalization. Given that abnormal LFTs are associated with worse mortality in ADHF during hospitalization, obtaining these tests prior to any intervention in the ED can further inform prognosis after receiving treatment. Prospective studies must be conducted to evaluate which patients would benefit from LFTs in terms of earlier diagnosis and risk stratification.

Our study has several limitations. First, this was a retrospective analysis of ED patients at a single site, which are susceptible to inherent limitations in data collection and study design. Additionally, our study used data from a single tertiary clinical medical center, which may not be generalizable to other emergency departments in other academic or community settings. We do

not have baseline LFTs for this group of patients, so it is possible that patients with chronic HF had preexisting abnormal LFTs. We also did not have baseline renal function for patients in our dataset which represents a group where BNP might be elevated in the absence of overt heart failure. However, the intention of our analysis was to capture real world ED setting where this information might not always be accessible. We did not systematically obtain LFTs for all potentially eligible patients, and a substantial number of patients did not have LFTs obtained in the ED. Patients with missing LFTs had higher odds of final ADHF diagnosis at discharge, similar to patients with abnormal LFTs. A plausible explanation for this finding is that ED clinicians were less likely to order LFTs if they had a high degree of certainty that a patient was presenting with ADHF. This finding makes it difficult to interpret the outcome in patients with missing LFTs, because these patients potentially might have had abnormal LFTs if the tests were obtained. However, other studies, such as ADHERE-HF[33], had similar proportions of missing LFTs to our study. This finding in itself is interesting in that it suggests that providers may have been relying more heavily on other forms of diagnostic testing, such as echocardiogram, when LFTs might have given a more cost effective insight into volume status or effective circulating volume. An important study done by Vyskocilova et al examined a large repository of patients with ADHF across 9 university hospitals and 5 regional health care facilities in the Czech Republic. They found that abnormal LFTs were found in 76% of patients with ADHF and patients with cardiogenic shock were more likely to have abnormal LFTs than those with mild ADHF or pulmonary edema[34]. They found that abnormal LFTs were highly suggestive of more severe ADHF and reflected worse NYHA class. They argued that it is crucial to assess LFTs in the initial diagnostic investigation of ADHF as it informs management and stratifies patients based on severity. Although patients with missing LFTs were similarly diagnosed with ADHF to

those with abnormal LFTs, it is possible that LFTs performed in the ED would have facilitated any additional work up performed after admission.

On the other hand, our study has important strengths, especially in contrast to prior analyses. First, we studied a large sample of patients seen in the ED prior to admission, where an initial suspicion for ADHF is most crucial to guide early evidence-based diagnosis and management. For these reasons, the study is generalizable to patients presenting to the ED with similar complaints and available lab tests. Second, our study was powered to adjust for BNP, which is known to be a strong predictor of ADHF. Third, our study estimated LRs, a key step in translating diagnostic test findings to clinical practice.

Our real-world analysis of patients admitted from the ED with suspected ADHF found that LFTs were not ordered for 40% of patients. Among patients who had LFTs ordered, abnormal LFTs in the ED are associated with a final ADHF diagnosis, the LRs indicate their limited diagnostic value, particularly in contrast with BNP. To balance the risks of overuse of tests and high inpatient mortality associated with abnormal LFTs, it is imperative to prospectively evaluate LFTs in the workup of ADHF and incorporate recommendations in society guidelines for clinical practice.

Figure 1. Classification Tree

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Table 1. Baseline Characteristics of Patients with Suspected ADHF in the Emergency Department

Characteristic	LFTs – Normal Range N=1,342	LFTs - Abnormal Range N=1,842	LFTs – Missing N=2,139	P value[a]
Age at ED visit – mean in years+/-SD	71 +/-16	67 +/-16	68 +/-16	<0.001
Sex Identified – No.(%)				
Male	633 (47%)	1,036 (56%)	1,113 (53%)	<0.001
Female	709 (53%)	806 (44%)	1,026 (48%)	
Race and Ethnicity – No.(%)				
Non-Hispanic Asian	303 (23%)	459 (25%)	442 (21%)	<0.001
Non-Hispanic Black or African American	236 (18%)	375 (20%)	401 (19%)	
Non-Hispanic White	546 (41%)	658 (36%)	918 (43%)	
Hispanic, any race	134 (10%)	202 (11%)	181 (9%)	
Other	108 (8%)	132 (7%)	174 (8%)	
Unknown/Declined to state	15 (1%)	16 (1%)	20 (1%)	
Insurance[b] No.(%)				
Private	147 (11%)	274 (13%)	295 (14%)	<0.001
MediCal	218 (16%)	382 (21%)	367 (17%)	
Medicare	927 (69%)	1,086 (59%)	1,357 (64%)	
Other	49 (4%)	23 (1.3%)	117 (5%)	
Diuretics in the ED?				
Yes	250 (19%)	449 (24%)	483 (23%)	0.001
No	1,092 (81%)	1,393 (76%)	1,656 (77%)	
BNP* in the ED?				
High BNP (>700mg/dL)	308 (23%)	636 (35%)	618 (29%)	<0.001
Intermediate High BNP(300-700mg/dL)	278 (21%)	357 (19%)	441 (21%)	
Intermediate Low BNP(100-300 mg/dL)	339 (25%)	376 (20%)	455 (21%)	

Low BNP (<100 mg/dL)	417 (31%)	473 (26%)	625 (29%)	
Past Medical History				
History of Asthma	251 (19%)	244 (13%)	379 (18%)	<0.001
History of COPD	345 (26%)	412 (22%)	580 (27%)	0.002
History of Smoking	699 (52%)	928 (50%)	1,129 (53%)	0.012
ED Diagnosis**				
ADHF†	107 (8%)	274 (15%)	281 (13%)	<0.001
Pneumonia	175 (13%)	243 (13%)	330 (15%)	0.025
COPD exacerbation	124 (9%)	96 (5%)	235 (11%)	<0.001
Asthma exacerbation	27 (2%)	28 (2%)	68 (3%)	0.001
Acute Upper Respiratory Infection	2 (0.2%)	1 (0.1%)	8 (0.4%)	0.028
Any Liver Pathology‡	12 (1%)	107 (6%)	16 (1%)	<0.001
Final Discharge Diagnosis°				
ADHF	283 (21%)	549 (30%)	622 (29%)	<0.001
Not ADHF	1,059 (79%)	1,293 (70%)	1,517 (71%)	

[a]P values based on Chi Square analysis for categorical variables and ANOVA for continuous variables
[b]Insurance is categorized as "Private" (Aetna, Blue Cross, Blue Shield, GCSS/GHP, Capitation, Charity, Commercial, Covered California, Covered California – MediCal, HealthNet, Institutional, and Kaiser), "MediCal" (Medicaid/MIA/CMSP, MediCal managed care, MediCal pending, MediCal standard) "Medicare" (Medicare, Medicare Advantage HMO/Senior, Medicare Advantage PFFS) and "Other" (Self-pay, United Health Care, Worker's compensation)
*BNP=Brain Natriuretic Peptide
**ED Diagnosis was obtained through specification of ICD10 codes for respiratory diagnoses and liver-related diseases
†ADHF=Acute Decompensated Heart Failure
‡Any liver pathology includes ICD10 codes for the following: alcoholic liver disease, toxic liver disease, hepatic failure (not elsewhere specified), chronic hepatitis (not elsewhere specified), fibrosis and cirrhosis of liver, other inflammatory liver diseases, other diseases of the liver, liver disorders in diseases of the liver (classified elsewhere)
¶Suspected ADHF is defined as patients who had a BNP ordered in the ED
°Final discharge diagnosis of ADHF is based on ICD 10 codes for a diagnosis of heart failure named on the discharge summary for a patient's specific encounter

Table 2. Liver Function Tests, BNP and Acute Decompensated Heart Failure at Discharge in ED patients with suspected ADHF (n=5,323)

Characteristic	N	% with ADHF diagnosis at discharge	p-value*	LR(95% CI)
Liver Function Tests (LFTs)				
Abnormal LFTs	1,842	30%	0.000	1.20 (1.13-1.28)
Normal LFTs	1342	21%		0.76 (0.68-0.84)
Missing LFTs	2139	29%		-
Alanine Transaminase (ALT)				
ALT >=100 mg/dL	168	27%	0.017	1.03 (0.74-1.44)
ALT 34-99 mg/dL	684	30%		1.19 (1.03-1.37)
ALT <34 mg/dL	2,310	25%		0.95 (0.90-1.00)
Missing ALT	2,161	29%		-
Aspartate Transaminase (AST)				
AST>=100 mg/dL	246	24%	0.000	0.87 (0.66-1.16)
AST 34-99 mg/dL	1,070	30%		1.22 (1.10-1.35)
AST <34 mg/dL	1,864	24%		0.90 (0.84-0.97)
Missing AST	2,143	29%		-
Alkaline Phosphate (AlkPhos)				
AlkPhos >=200 mg/dL	249	22%	0.004	0.81 (0.60-1.08)
AlkPhos 123-199 mg/dL	420	31%		1.26 (1.04-1.53)
AlkPhos <123 mg/dL	2,451	26%		0.98 (0.94-1.02)
Missing AlkPhos	2,203	29%		-
Total Bilirubin				
Total Bilirubin>2mg/dL	323	32%	0.000	1.32 (1.06-1.65)
Total Bilirubin 1.2-2 mg/dL	501	36%		1.59 (1.35-1.88)
Total Bilirubin<1.2 mg/dL	2,314	23%		0.85 (0.81-0.90)
Missing Total Bilirubin	2,185	29%		-
Direct Bilirubin				
Direct Bilirubin>2 mg/dL	18	22%	0.007	0.62 (0.22-1.75)
Direct Bilirubin 0.3-2 mg/dL	48	48%		1.99 (1.32-3.00)

Direct Bilirubin<0.3 mg/dL	51	20%		0.53 (0.30-0.93)
Missing Direct Bilirubin	5,206	27%		-
BNP**				
High BNP (>700mg/dL)	1,562	53%	0.000	2.95(2.72-3.19)
Intermediate High BNP(300-700mg/dL)	1,076	35%		1.42(1.28-1.59)
Intermediate Low BNP(100-300 mg/dL)	1,170	16%		0.51(0.44-0.59)
Low BNP (<100 mg/dL)	1,515	5%		0.13(0.10-0.17)

*P-values are based on Chi-Square test
**BNP=Brain Natriuretic Peptide

Table 3. Univariate and Multivariate Logistic Regression Analysis of High LFTs and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5,323)

Characteristic	Univariate Analysis	Multivariate Analysis*

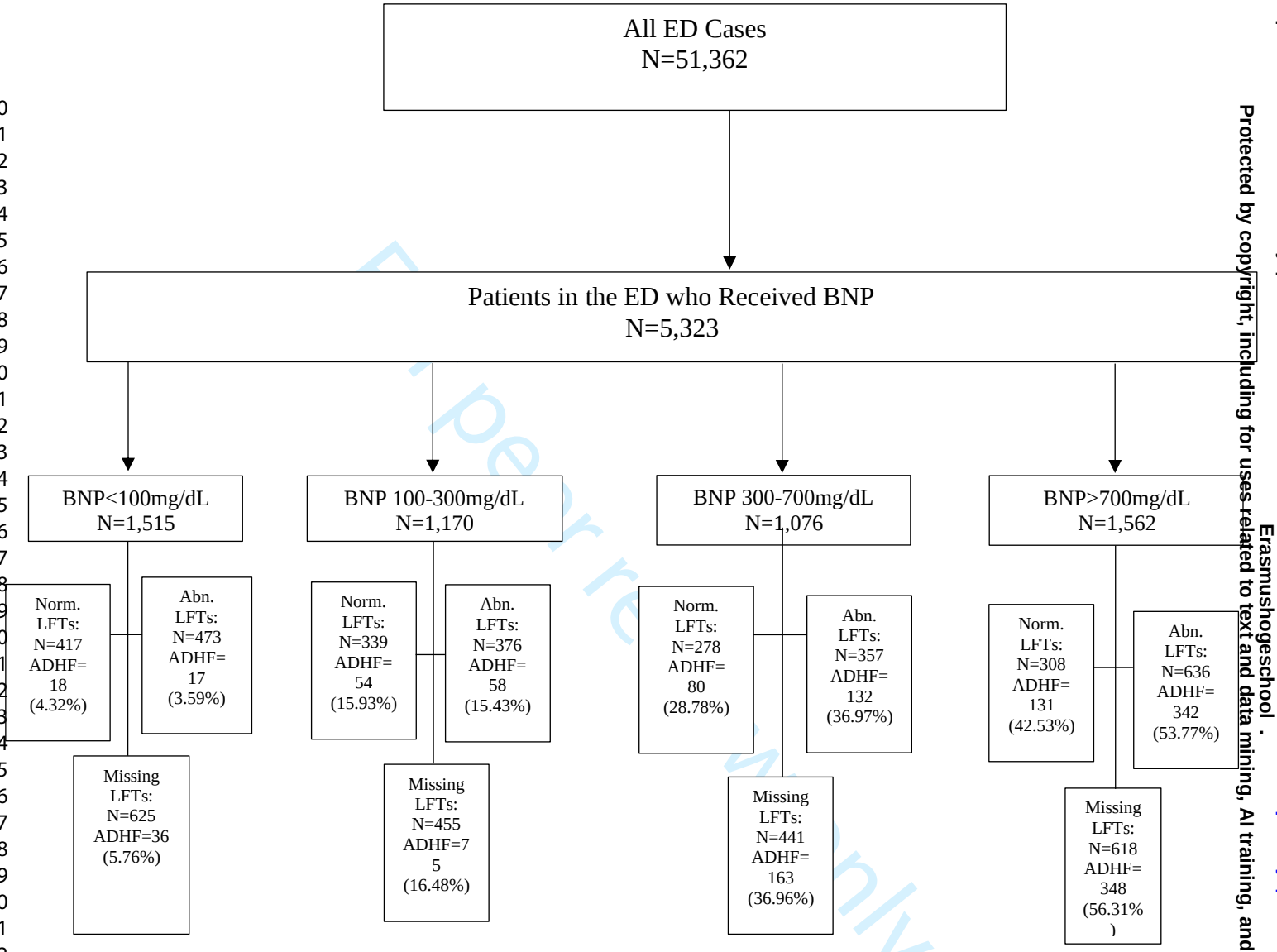
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Abnormal LFTs	1.59(1.35-1.87)	0.000	1.29 (1.08-1.55)	0.006
Missing LFTs	1.53(1.31-1.80)	0.000	1.42 (1.19-1.71)	0.000
Normal LFTs	Reference	Reference	Reference	Reference
BNP**				
High BNP (>700mg/dL)	22.53(17.41-29.17)	0.000	22.53 (17.35-29.28)	0.000
Intermediate High BNP(300-700mg/dL)	10.88(8.31-14.24)	0.000	11.10 (8.45-14.60)	0.000
Intermediate Low BNP (100-300 mg/dL)	3.87(2.91-5.14)	0.000	4.00 (3.00-5.33)	0.000
Low BNP(100 mg/dL)	Reference	Reference	Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65-1.01)	0.062
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.12)	0.438
Other, Non-Hispanic			1.06 (0.80-1.41)	0.695
Hispanic, any race			0.97 (0.74-1.26)	0.809
Unknown/Declined to state			0.52 (0.21-1.25)	0.144
Age at ED visit, per year			1.00 (0.99-1.00)	0.395
Male sex			1.21(1.06-1.39)	0.006

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Figure 1. Classification Tree



Appendix:

Appendix Table 1. Univariate and Multivariate Logistic Regression Analysis of High ALT and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
ALT>100 mg/dL	1.09(0.76-1.55)	0.638	1.01 (0.68-1.50)	0.966
ALT 34-99 mg/dL	1.26(1.04-1.52)	0.018	1.22 (0.98-1.50)	0.072
ALT<34 mg/dL	Reference	Reference	Reference	Reference
Missing ALT	1.21 (1.06-1.38)	0.005	1.26 (1.08 -1.46)	0.002
High BNP (>700mg/dL)			22.96 (17.68-29.82)	0.000
Intermediate High BNP(300-700mg/dL)			11.21 (8.53-14.73)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.02 (3.02-5.36)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65-1.01)	0.064
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.92 (0.76-1.12)	0.422
Other, Non-Hispanic			1.03 (0.77-1.37)	0.846
Hispanic, any race			0.97 (0.74-1.26)	0.807
Unknown/Declined to state			0.50 (0.21-1.23)	0.132
Age at ED visit			1.00 (0.99-1.00)	0.201
Male Sex			1.21(1.06-1.39)	0.005

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 2. Univariate and Multivariate Logistic Regression Analysis of High AST and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
AST>100 mg/dL	0.97 (0.71-1.32)	0.831	1.02 (0.71-1.43)	0.961
AST 34-99 mg/dL	1.35 (1.15-1.60)	0.000	1.15 (0.95 -1.39)	0.144
AST<34 mg/dL	Reference	Reference	Reference	Reference
Missing AST	1.28 (1.11-1.48)	0.001	1.28 (1.09-1.50)	0.002
High BNP (>700mg/dL)			22.82 (17.56 - 29.63)	0.000
Intermediate High BNP(300-700mg/dL)			11.17 (8.50-14.67)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.01 (3.01-5.35)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.82 (0.66-1.02)	0.069
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.13)	0.453
Other, Non-Hispanic			1.04 (0.80-1.41)	0.810
Hispanic, any race			0.97 (0.75-1.27)	0.842
Unknown/Declined to state			0.51 (0.21-1.25)	0.140
Age at ED visit			1.00 (0.99-1.00)	0.295
Male Sex			1.22(1.06-1.40)	0.004

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 3. Univariate and Multivariate Logistic Regression Analysis of High AlkPhos and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)*

Characteristic	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
AlkPhos>200 mg/dL	0.82(0.60-1.13)	0.222	0.80 (0.56-1.12)	0.201
AlkPhos 123-199 mg/dL	1.29(1.03-1.61)	0.029	1.03 (0.56-1.13)	0.801
AlkPhos<123 mg/dL	Reference	Reference	Reference	Reference
Missing AlkPhos	1.19(1.05-1.36)	0.007	1.21 (1.05-1.40)	0.009
BNP**				
High BNP (>700mg/dL)			22.97 (17.68-29.84)	0.000
Intermediate High BNP(300-700mg/dL)			11.16 (8.49-14.67)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.00 (3.00-5.33)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.82 (0.66 -1.02)	0.077
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.14)	0.439
Other, Non-Hispanic			1.03 (0.78 -1.38)	0.819
Hispanic, any race			0.98 (0.75-1.27)	0.868
Unknown/Declined to state			0.51 (0.21 -1.25)	0.142
Age at ED visit			1.00 (0.99-1.00)	0.246
Male Sex			1.22(1.07-1.40)	0.004

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 4. Univariate and Multivariate Logistic Regression Analysis of High DBili and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
DBili>2 mg/dL	1.17(0.32-4.34)	0.813	1.37 (0.33-5.67)	0.667
DBili 0.3-2 mg/dL	3.77(1.54-9.22)	0.004	3.63 (1.32-10.03)	0.013
DBili<0.3 mg/dL	Reference	Reference	Reference	Reference
Missing DBili	1.53(0.77-3.07)	0.227	1.45 (0.68-3.10)	0.341
BNP**				
High BNP (>700mg/dL)			22.86 (17.60 - 29.69)	0.000
Intermediate High BNP(300-700mg/dL)			11.17 (8.50 - 14.68)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.01 (3.01-5.35)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65 -1.01)	0.062
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.93 (0.77-1.12)	0.450
Other, Non-Hispanic			1.03 (0.77-1.37)	0.838
Hispanic, any race			0.95 (0.74-1.25)	0.759
Unknown/Declined to state			0.50 (0.21-1.23)	0.131
Age at ED visit			1.00 (0.99-1.00)	0.298
Male Sex			1.22(1.07-1.40)	0.004

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

Appendix Table 5. Univariate and Multivariate Logistic Regression Analysis of High LFTs and Final Diagnosis of ADHF in patients with suspected ADHF in the ED (n=5,323)

Characteristic	**Univariate Analysis**		**Multivariate Analysis***	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
TBili>2 mg/dL	1.55 (1.20-2.00)	0.001	1.36 (1.10-1.75)	0.036
TBili 1.2-2 mg/dL	1.87 (1.52-2.30)	0.000	1.39 (1.02-1.82)	0.005
TBili<1.2 mg/dL	Reference	Reference	Reference	Reference
Missing TBili	1.40 (1.22-1.60)	0.000	1.38 (1.19-1.60)	0.000
BNP				
High BNP (>700mg/dL)			22.51 (17.32 - 29.44)	0.000
Intermediate High BNP(300-700mg/dL)			11.13 (8.46 - 14.64)	0.000
Intermediate Low BNP (100-300 mg/dL)			4.00 (3.00-5.33)	0.000
Low BNP(100 mg/dL)			Reference	Reference
Race and Ethnicity†				
Non-Hispanic Asian			0.81 (0.65 -1.01)	0.061
Non-Hispanic Black or African American			Reference	Reference
Non-Hispanic White			0.92 (0.76-1.11)	0.373
Other, Non-Hispanic			1.03 (0.78-1.37)	0.827
Hispanic, any race			0.95 (0.73-1.24)	0.732
Unknown/Declined to state			0.50 (0.21-1.22)	0.129
Age at ED visit			1.00 (0.99-1.00)	0.198
Male Sex			1.21(1.05-1.38)	0.007

*Multivariate analysis adjusted for BNP, age at ED visit, race and ethnicity

**BNP in the multivariate analysis reflects analysis of highLFTs, race and ethnicity and age at ED visit

†Univariate analyses of "Race and ethnicity" and "Age at ED visit" were not performed

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5,6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6,7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	6,7, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	6,7,8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6,7,8, Table 2,3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title page (page 1) Abstract (pages 1, 2)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Pages 3,4,5
Objectives	3	State specific objectives, including any prespecified hypotheses			Pages 4,5
Methods					
Study Design	4	Present key elements of study design early in the paper			Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Pages 5,6,7

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Pages 5, 6. A complete list of codes for exposures and outcomes is readily available.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Pages 5,6,7

Bias	9	Describe any efforts to address potential sources of bias			Not applicable
Study size	10	Explain how the study size was arrived at			Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			Pages 5,6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			Page 7
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 7

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Not applicable
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Pages 5,6,7, Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			Pages 7,8, Table 1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure			Pages 7,8,9, Tables 2,3

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Pages 7,8,9, Tables 2,3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Page 9
Discussion					
Key results	18	Summarise key results with reference to study objectives			Pages 9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Pages 2,3,13,14
Interpretation	20	Give a cautious overall interpretation of results considering objectives,			Pages 13

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			Page 14
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			Pages 14,15
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 15

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.