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Direct Comparison of High-Sensitivity Cardiac Troponin T and I for Prediction of Mortality in Patients with Pneumonia

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Abstract

Objectives: The primary objective was to directly compare the prognostic accuracy of hs-cTnT versus hs-cTnI for the prediction of death in patients with pneumonia.

Methods: The prognostic accuracy of high sensitivity (hs)-cTnT and hs-cTnI was directly compared among patients presenting with dyspnea to the emergency department and centrally adjudicated by two independent experts to have pneumonia. Blood samples for the blinded measurement of hs-cTnT and hs-cTnI, as well as NT-proBNP were obtained at ED presentation. CURB-65 was calculated as the multivariate risk score recommended in current guidelines. Primary endpoints were all-cause and cardiovascular (CV) mortality at 1 year.

Results: Among 306 patients, median age was 75 years, 38% were women, with extensive comorbidities including chronic obstructive pulmonary disease (COPD) in 41% and chronic heart failure (HF) in 26%. Cumulative 1-year all-cause mortality was 26.8% (82 deaths) and cumulative 1-year CV mortality was 9.5% (29 CV-deaths). While both hs-cTnT and hs-cTnI were independent predictors of death, the prognostic accuracy of hs-cTnT as quantified by the area under the curve (AUC) was significantly higher than hs-cTnI for 1-year all-cause mortality (AUC 0.73, 95%CI 0.66-0.779 vs. AUC 0.66, 95%CI 0.59-0.72; p=0.003) and CV-death (AUC 0.82, 95%CI 0.76-0.88 vs. 0.72, 95%CI 0.64-0.80; p=0.006), and comparable to NT-proBNP (AUC 0.72, 95%CI 0.59-0.72 and AUC 0.84, 95%CI 0.78-0.90 respectively, both p=ns). Compared to CURB-65 (AUC 0.60), the prognostic accuracy of hs-cTn was similar (hs-cTnI, p=0.463) or even higher (hs-cTnT, p=0.003).

Conclusions: Hs-cTnT has high prognostic accuracy and is superior to hs-cTnI in the prediction of all-cause and CV-mortality in patients with pneumonia.

Keywords: Pneumonia; Hs-cTnT; Hs-cTnI; NT-proBNP; Comparison; Mortality; Biomarkers.

Abbreviations: AUC: Area Under The Curve; BMI: Body Mass Index; BNP: B-Type Natriuretic Peptide; CI: Confidence Interval; CURB-65: Confusion Blood Urea Respiratory rate Blood Pressure and Age ≥ 65; CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; cTn: Cardiac Troponin; CV: Cardiovascular; ED: Emergency Department; EDTA: Ethylenediaminetetraacetic Acid; HF: Heart Failure; HR: Hazard Ratio; IQR: Interquartile Range; LoD: Limit of Detection; NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide; ROC: Receiver Operated Characteristics.

Introduction

Pneumonia is a common reason for presentation to the emergency department (ED) associated with substantial short and long-term mortality with more than 4 million deaths worldwide annually. The pathophysiological link between pneumonia and death is incompletely understood [1-3]. Recent studies indicate an increased risk for acute myocardial infarction and acute heart failure (HF) among patients with pneumonia provided evidence for the heart as a possible contributor [4-8]. In addition, pilot studies have documented that hemodynamic cardiac stress as quantified by B-type natriuretic peptide (BNP) and NT-proBNP, and cardiomyocyte injury as quantified by cardiac troponin (cTn) T and I seem increased and are associated with mortality in patients with pneumonia [4-11]. These biomarkers may be useful in the early and rapid risk-stratification of patients with pneumonia and may complement or even replace at times complex multivariable risk scores [12-15]. It is unknown, which of the

biomarkers quantifying cardiomyocyte injury, cTnT or cTnI, should be preferred in the prediction of mortality in patients with pneumonia. With the development of high-sensitivity (hs) cTn assays, several studies demonstrated that, there are pathophysiological and analytical differences between hs-cTnT and hs-cTnI [16]. First, hs-cTnT plasma concentrations exhibit a diurnal rhythm, while hs-cTnI does not [16,17]. Second, hs-cTnI seems to be released from injured cardiomyocytes slightly earlier and possibly by less intense injury as compared to hs-cTnT [18]. Third, the association with renal dysfunction is stronger for hs-cTnT vs. cTnI [19]. Fourth, hemolysis common in blood samples taken in the ED, seems to slightly increase hs-cTnI concentration, but decrease hs-cTnT concentration [20,21]. Fifth, chronic skeletal muscle disease has been described as a non-cardiac cause of hs-cTnT, but not hs-cTnI elevations [22]. Therefore, the aim of this study was to directly compare the prognostic performance of hs-cTnT and hs-cTnI in patients presenting with pneumonia to the ED.

Materials and Methods

Study design and study population

This is a secondary analysis of the Basics in Acute Shortness of Breath Evaluation (BASEL V) study (NCT01831115). BASEL V was a prospective, multicentre, diagnostic study enrolling adult patients presenting with non-traumatic acute dyspnea to the ED of two university hospitals (Basel and Zurich, Switzerland) from May 2006 to January 2013 [23-26]. Patients were eligible if they were capable of providing written informed consent. Accordingly, patients in shock and/or severe respiratory failure and patients with terminal kidney failure on chronic dialysis were excluded. Written informed consent was obtained from all participating patients. The study was approved by the local ethics committee in Basel (EK 52/02) and Zürich (EK 2001-0315) and carried out according to the principles of the Declaration of Helsinki. For this analysis, all patients with a final diagnosis of pneumonia were included. Management of patients was at the discretion of the treating physician, followed current clinical practice guidelines [1-3,27] and was not affected by this study.

Diagnosis of pneumonia

Two independent internists/cardiologists adjudicated the final cause of acute dyspnea including pneumonia using all available information pertaining to individual computed tomography of the chest, X-ray, clinical signs and symptoms, laboratory results and 90 days follow-up. The definition of pneumonia was according to criteria from Fine et al. and Leroy et al. [28,29] and comprised a new onset of pulmonary infiltrate on chest X-ray or computed tomography in combination at least one pneumonia-related symptom such as cough, fever, dyspnea, and/or chest pain. In case of disagreement, a third internist/cardiologist reviewed the case and adjudicated the final diagnosis.

Follow-up and endpoints

Patients were contacted after 90 days and 1 year by telephone calls or in written form by trained researchers. In case of a possible clinical event, further information was obtained from the hospital, general physician or the national death registry records. The co-primary endpoints were all-cause death and cardiovascular (CV) death, the latter being defined as death attributable to acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage and other cardiovascular causes like pulmonary embolism within one year. Unless evidence of a non-cardiovascular cause was available, all fatalities were presumed to be cardiovascular in nature [30].

Analysis of blood biomarkers

Blood samples in Ethylenediaminetetraacetic acid (EDTA-plasma) were collected for each patient at presentation. Directly after collection, samples were centrifuged and frozen at -80°C until assayed. High-sensitivity cTnT (Roche Elecsys 2010, Roche Diagnostics) was measured with a LoD (limit of detection) of 5 ng/L and 99th percentile of a healthy reference population at 14 ng/L. High-sensitivity cTnI was measured using the Erenna system (Singulex Inc. Alameda, USA), which has even more than 20-times higher analytical sensitivity as compared to hs-cTnT with a LoD of 0.1 ng/L and 99th percentile of 10.1 ng/L [31]. NT-proBNP was measured using the Elecsys proBNP assay (Elecsys proBNP, Roche Diagnostics AG, Zug, Switzerland). Measurement ranges from 5 to 35 000 pg/mL with a LoD of 5 pg/mL and a coefficient of variation of 5.7% at 64 pg/mL. The laboratory technicians who measured hs-cTnT, hs-cTnI, and NT-proBNP were blinded to patient data. C-reactive protein (CRP) was measured locally as part of the routine ED care (reference value<10 mg/L).

Statistical analysis

The primary objective was to directly compare the prognostic accuracy of hs-cTnT vs. hs-cTnI. Secondary objectives included the comparison of hs-cTnT and hs-cTnI with NT-proBNP, the comparison with CRP and the comparison with CURB-65 (Confusion, Blood Urea, Respiratory rate, Blood Pressure and Age ≥ 65) the multivariable risk score recommended in current guidelines for the prediction of 30-day mortality [32]. Continuous variables are presented as median and interquartile range (IQR) and categorical variables as absolute numbers and percentages. Baseline characteristics were compared using the Mann-Whitney U test for continuous variables and the Pearson chi square test for categorical variables. Time dependent areas under the receiver operating characteristic curve (AUC) were used to quantify the predictive accuracy (discriminative ability) of the biomarkers for all-cause mortality within one year, whilst accounting for censoring [33] based on the weighted Kaplan-Meier estimator (timeROC package, R). Multivariable Cox regression was used to assess whether the biomarkers were predictors for all-cause mortality and CV death independent of age, male gender, history of coronary artery disease (CAD), history of HF, chronic renal insufficiency and antiplatelet therapy. These variables were selected based on possible interaction with the investigated biomarkers [6]. Biomarkers were Log2 transformed and correlation and variance inflation factors were calculated. Kaplan-Meier curves for patients stratified by biomarker tertiles were compared using log-rank testing. Subgroups analyses were completed in patients with or without an additional adjudicated diagnosis of acute HF. This was an exploratory analysis within a prospective study, and sample size of the overall cohort was not determined specific for this analysis. [23-26] Statistical analyses were performed with SPSS version 25.0 and R version 3.4.4. All hypothesis testing were two-tailed, and a p-value<0.05 was considered statistically significant.

Results

Overall, 306 patients with an adjudicated diagnosis of pneumonia were eligible for analysis (Figure 1). Median age was 75 (IQR 63-81)

years, 38% were women, and the most patients had several comorbidities including chronic obstructive pulmonary disease (COPD) in 41% and HF in 26% (Table 1). Supplementary Table 1 shows the baseline characteristics of the initial pneumonia cohort including those patients with unavailable biomarker measurements. The final adjudicated diagnosis was pneumonia in 155 patients (50.7%), pneumonia combined with acute HF in 112 patients (36.6%), and pneumonia combined with exacerbated COPD in 39 patients (12.7%). Median follow-up time was 727 (IQR 275-919) days. Cumulative 30-days all-cause mortality and cumulative 30-days CV mortality was 31 (10.1%) and 7 (2.3%) respectively. Additionally, 1-year all-cause mortality was 26.8% (82 deaths) and cumulative 1-year CV mortality was 9.5% (29 CV deaths).

Variables	All Patients (n=306)	Survivors (n=225)	Deceased (n= 82)	p-value*
Age (years)	75 (63-81)	73 (60.7-80)	78 (69-85)	<0.0001
Female gender (%)	115 (37.6%)	92 (30.7%)	23 (7.5%)	0.037
BMI (kg/m^2)	24.9 (21.5-29.1)	25.56 (21.7-29.6)	23.87 (20.4-27.4)	0.012
Heart rate (bpm)	97 (83-11)	96 (83-111)	97 (80.5-111.5)	0.937
Systolic blood pressure (mmHg)	131 (115-145)	133 (117-148)	128 (109.5-140)	0.009
Diastolic blood pressure (mmHg)	72 (63-87)	73.50 (63.7-87)	69 (61.5-85.5)	0.307
Pulse oximetry (%)	94 (90-96)	94 (90-96)	94 (88-96.2)	0.609
Creatinine (µmol/l)	86 (67-127.8)	83 (65.2-110)	105 (75.8-162.6)	0.051
eGFR CKD-EPI (mL/min/1.73 m^2)	72.4 (45-88.2)	74.83 (50.8-91.9)	52.26 (28.4-84)	0.0003
Comorbidities				
Heart failure (%)	79 (25.8%)	53 (23.8%)	26 (32.1%)	0.143
CAD (%)	97 (31.7%)	67 (29.9%)	30 (36.6%)	0.266
Myocardial infarction (%)	53 (17.3%)	38 (17%)	15 (18.8%)	0.718
Atrial Fibrillation (%)	72 (23.5%)	49 (21.9%)	23 (28%)	0.259
Stroke (%)	35 (11.4%)	20 (8.9%)	15 (18.3%)	0.023
Peripheral vascular disease (%)	44 (14.4%)	31 (14.2%)	13 (16.3%)	0.651
Chronic kidney disease (%)	86 (28.1%)	52 (23.2 %)	34 (42%)	0.001
COPD (%)	124 (40.5%)	92 (41.1%)	32 (39.0%)	0.747
Cardiovascular Risk Factors				
Hypertension (%)	204 (66.5%)	145 (64.7%)	59 (72%)	0.235
Smoking status:				0.268
Never smoker (%)	77 (25.2%)	59 (76.6%)	18 (23.4%)	
Active smoker (%)	67 (21.9%)	53 (24.1%)	14 (17.7%)	
Former smoker (%)	155 (50.7%)	108 (49.1%)	47 (59.5%)	
Diabetes mellitus (%)	71 (23%)	51 (22.8%)	20 (24.4%)	0.766
Dyslipidemia (%)	115 (37.6%)	82 (37.3%)	33 (40.7%)	0.583

Data are presented as absolute number and (%) or median and (Q1-Q3). *for the comparison of deceased patients versus survivors. BMI=body mass index, COPD=chronic obstructive pulmonary disease, CAD=coronary artery disease

Table 1: Baseline characteristics of the 306 patients presenting with pneumonia included in this cohort.

Hs-cTnT and hs-cTnI concentrations at ED presentation

Compared to survivors, patients who died within 1 year after presentation had significantly higher hs-cTnT concentrations (47 ng/L [Interquartile Range (IQR) 27.5-81]) vs. 20 ng/L [IQR 12-37], respectively p<0.001), hs-cTnI concentrations (12.7 ng/L [IQR 6.26-58.2]) vs. 6.9 ng/L [IQR 3.1-17.8], p<0.001), and NT-proBNP concentrations (4096 pg/mL [IQR 1005-9017] vs. 850 pg/mL [IQR

252-3446], p<0.001). Conversely, CRP concentrations were similar in deceased patients (97 mg/L, [IQR 39.8-181.6) and in survivors (100.9 mg/L [IQR 34.8-207.7], p=0.760). Overall, 75.2% of patients had elevated hs-cTnT concentrations (>14 ng/L), while only 44.8% of patients had hs-cTnI concentrations above the 99th-cut off (>10.1 ng/L). Hs-cTnT and hs-cTnI correlated strongly with each other (Spearman's rho=0.819), as well as with NT-proBNP concentrations (Spearman's rho=0.692 and Spearman's rho=0.666) all p<0.001 (Supplementary Table 2).

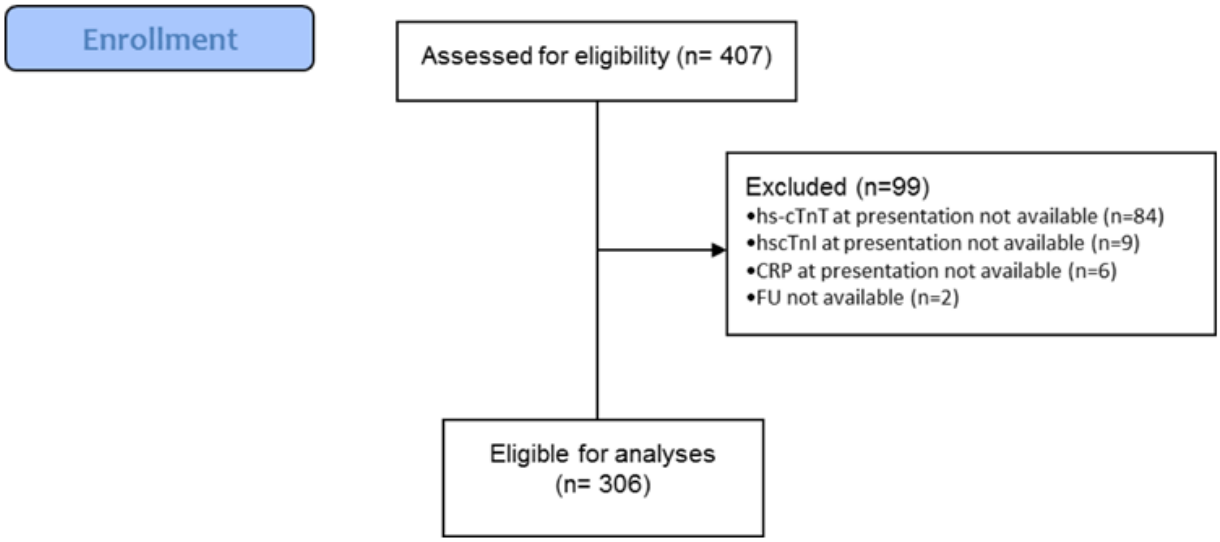

Figure 1: Study flow diagram.

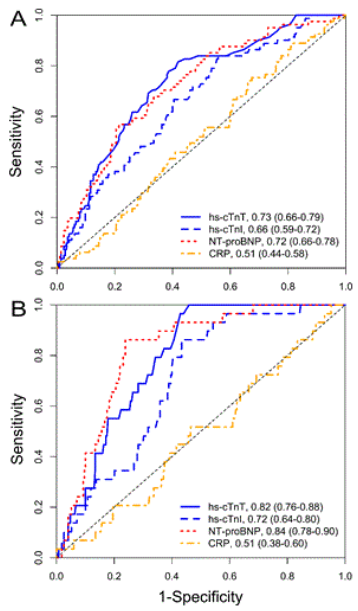

Figure 2: Receiver operator curves (ROCs) quantifying prognostic accuracy for 1-year all-cause (Figure 2A) and cardiovascular mortality (Figure 2B).

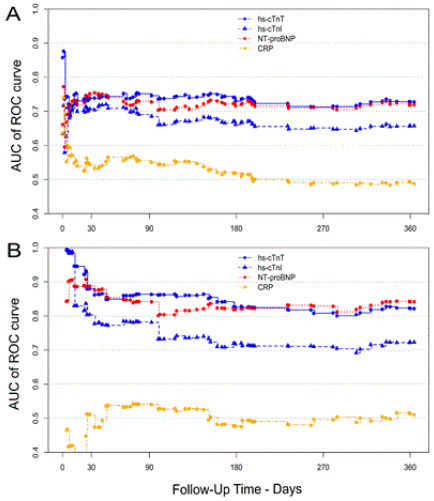

Figure 3: Predictive discrimination of the biomarker concentrations at ED presentation for all-cause death (Figure 3A) and cardiovascular death (Figure 3B) within 1 year in patients presenting with pneumonia.

Prediction of mortality

Cox-regression analysis showed a hazard ratio of death within one year for log transformed hs-cTnT [HR] of 1.37 (95% CI 1.20-1.57, p<0.001). Similarly, hs-cTnI ([HR] 1.17, 95% CI 1.07-1.28, p=0.001) and NT-proBNP ([HR] 1.30, 95% CI 1.15-1.48, p<0.001), but not CRP

([HR] 1.05, 95% CI 0.92-1.19, p=0.470) remained independent predictors for 1-year mortality when adjusted for age, sex, history of CAD, history of HF, antiplatelet therapy and chronic renal insufficiency.

Direct comparison of cTnT vs. cTnI

The prognostic accuracy as quantified by the AUC of hs-cTnT was significantly higher than of hs-cTnI for 1-year all-cause mortality (0.73 vs. 0.66, p=0.003) and CV death (AUC 0.82 vs. 0.72, p=0.006), and comparable to NT-proBNP (0.72 and 0.84, respectively, both p=ns, Figure 2A/2B). All patients with CV-death at one year (29 in total) had elevated cTnT concentrations above the 99th percentile. Additionally, 28 (97%) out of these 29 patients had values of hs-cTnT at least twice the upper reference limit as described by the manufacturer. This was not the case for hs-cTnI with only 23 patients having elevated concentrations.

Time-dependent analysis revealed that the superiority of hs-cTnT vs. hs-cTnI was consistent throughout the entire follow-up period, for both all-cause (Figure 3A) and CV-mortality (Figure 3B). This finding was also consistent in the subgroups with or without an additional adjudicated diagnosis of acute HF (Supplemental Figure 1A and 1B). Figure 4 shows Kaplan-Meier curves for all-cause death and CV death (Figure 4A and 4B) stratified by hs-cTnT/I concentration tertiles with better discrimination of high-risk and moderate risk patients with hs-cTnT vs. hs-cTnI.

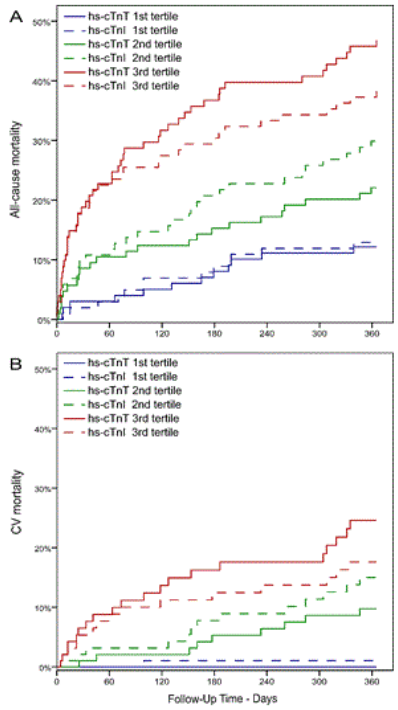

Figure 4: Cumulative all-cause mortality (A) and cardiovascular death (B) within one year of patients presenting with pneumonia. hs-cTnT and hs-cTnI levels at admission are categorized into tertiles: lower (green) intermediate (red) and upper (blue). Solid lines correspond to hs-cTnT and dotted lines to hs-cTnI.

Direct comparison with CURB-65

Variables required for calculation of the CURB-65 score were available in 232 (76%) patients. The cumulative incidence of death within 30 days was 9.9% (23 deaths) and the cumulative incidence of 1-year death was 27.4% (63 deaths). The prognostic accuracy of CURB-65, as quantified by the AUC was 0.63 (95% CI 0.52-0.74) for 30 days mortality and 0.60 (95% CI 0.53-0.67) for 1-year mortality (Supplemental Figure 2A and 2B), which was comparable to hs-cTnI (p=0.463) but lower than hs-cTnT (p=0.003).

Discussion

The aim of this study was to directly compare the prognostic performance of hs-cTnT and hs-cTnI in patients presenting with an adjudicated diagnosis of pneumonia to the ED. We report four major findings.

First, patients presenting to the ED with pneumonia have advance age and extensive cardiopulmonary comorbidities. Accordingly, 1-year mortality was very high. One of four patients died within one year. These findings extend and corroborate previous works [1,8,34,35] and highlight that the mortality of this population is comparable to patients presenting with acute HF or patients with cancer [27]. Apparently, the sole fact of requiring hospitalization and treatment due to pneumonia can be considered a sign of frailty and increased mortality risk [1,36].

Second, there are considerable differences in the prognostic performance of hs-cTnT and hs-cTnI in patients with pneumonia. While three-quarter of the patients have elevated hs-cTnT concentrations, hs-cTnI elevations were observed in less than half of patients. This difference is even more striking considering that the hs-cTnI assay used has a much higher analytical sensitivity as compared the hs-cTnT assay. This finding is in line with previous studies evaluating the prevalence of hs-cTnT and I elevations in patients admitted to the hospital for several clinical and surgical non-cardiac conditions [37,38]. Although both hs-cTnT and hs-cTnI concentrations were higher in deceased patients, as compared to survivors and independent predictors of death, hs-cTnT provided significantly higher prognostic accuracy for all-cause death and CV-death as compared to hs-cTnI. The exact pathophysiological mechanisms contributing to hs-cTnTs release from injured cardiomyocytes in patients with pneumonia are incompletely understood. However, pilot studies have suggested a role of ventilation-perfusion mismatch that might result in cardiac hypoxia, increased alveolar-arterial oxygen gradient leading to increased pulmonary artery pressure and to impaired right ventricular systolic function as assessed by echocardiography [9,39-41] In addition, evolving experimental evidence suggests possible differences in the local intra-cardiac release and clearance mechanisms for hs-cTnT and hs-cTnI beyond irreversible cardiomyocyte cell death [42]. These vital mechanisms may be adversely affected in patients with pneumonia and may have contributed to the superior prognostic performance of hs-cTnT vs. hs-cTnI.

Additionally, there was a strong correlation between hs-cTnT and hs-cTnI with NT-proBNP in this study. The fact that the correlation between hs-cTnT and NT-proBNP, age, serum creatinine, and eGFR was stronger as that of hs-cTnI may indicate that hs-cTnT concentrations more closely reflect and quantify also cardiac forward failure due to the inability of the heart to increase cardiac output to the extend required in sepsis due to pneumonia [6-8,40,43-46].

Third, hs-cTnT provided comparable prognostic accuracy to that of NT-proBNP, the current biochemical gold standard in the risk stratification of patients with pneumonia [6-8,40,43-46]. As measuring hs-cTnT is substantially less costly in most countries as compared to NT-proBNP, comparable prognostic accuracy combined with lower cost might well render hs-cTnT the preferred biochemical marker from a cost-effectiveness perspective.

Fourth, the findings of this study also challenge current classifications adjudicating the cause of death during follow-up, which classified less than 40% of deaths as CV, while hs-cTnT and NT-proBNP, as biomarkers quantifying cardiomyocyte injury and hemodynamic stress showed high accuracy in the prediction of both all-cause and CV-death. This discrepancy suggests that the heart plays a major role in the pathophysiology leading to death in many deaths assumed to be non-CV in nature. E.g. the inability of a sick heart to adequately meet the circulatory demands of another episode of severe sepsis could be essential in death from sepsis, although these deaths are classified as non-CV-death in current classification schemes.

This study has certain strengths. First, this was an unselected real-world ED cohort. Second, the first blood draw was performed at presentation and the results were blinded to the treating physicians.

This study also has limitations. First, this was a secondary analysis of the large prospective BASEL-V study. As such, no specific sample size calculation was performed. Second, as patients with severe renal dysfunction were excluded, we cannot comment on the preferred biomarker in these high-risk patients. Third, we cannot comment on the preferred biomarker in patients with pneumonia, who do not report dyspnea at presentation. It is conceivable, although unlikely, that other and/or additional mechanisms leading to cardiomyocyte injury affect the risk of death in these patients. Fourth, as an observational diagnostic study, BASEL-V did not interfere with patient management. Further studies are necessary to directly implement the hs-cTnT concentration into clinical decision-making. Possible consequences of detecting a high risk of death by elevated hs-cTnT concentrations include hospital admission, intense hemodynamic monitoring, cardiac work-up using echocardiography and possibly non-invasive stress imaging for functionally relevant CAD, and optimization of cardiovascular risk factors.

Conclusion

In conclusion, hs-cTnT, but not hs-cTnI, seems to be the preferred biomarker quantifying cardiomyocyte injury in the prediction of death among patients presenting with pneumonia to the ED.

Author Contributions

DF, JW, DW, TB, ZS, NK, JM, and CM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed substantially to the study design, data analysis, interpretation and/or the writing of the manuscript.

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