Myocardial injury in critically ill patients with community-acquired pneumonia

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Abstract

Background Myocardial injury, as reflected by elevated cardiac troponin levels in plasma, is common in patients with community-acquired pneumonia (CAP), but its temporal dynamics and etiology remain unknown. Our aim was to determine the incidence of troponin release in patients with CAP and identify risk factors which may point to underlying etiologic mechanisms.

Methods We included consecutive patients admitted with severe CAP to two intensive care units in the Netherlands between 2011 and 2015. High-sensitivity cardiac troponin I was measured daily during the first week. We used multivariable linear regression to identify variables associated with troponin release on admission, and mixed-effects regression to model the daily rise and fall of troponin levels over time.

Results Among 200 eligible patients, 179 were included, yielding 792 observation days. A total of 152 (85%) patients developed raised troponin levels >26 ng/L. Baseline factors independently associated with troponin release included coronary artery disease (160% increase, 95% CI 7-529), smoking (304% increase, 95% CI 59-924), and higher APACHE IV score (2% increase, 95% CI 0.7-3.3), whereas *Staphylococcus aureus* as a causative pathogen was protective (67% reduction, 95% CI 9-88). Time-dependent risk factors independently associated with daily increase in troponin concentrations included reduced platelet count (1.7% increase, 95% CI 0.1-3.4), tachycardia (1.6% increase, 95% CI 0.3-3), hypotension (5.1% increase, 95% CI 1-9.4) and dobutamine use (38.4% increase 95% CI 8.8-76).

Conclusions Cardiac injury develops in a majority of patients with severe CAP. Myocardial oxygen supply-demand mismatch and activated coagulation are potential causes of this injury.

Key-Words: Myocardial injury; Community-acquired pneumonia; Sepsis; Etiology

Background

Patients hospitalized for community-acquired pneumonia (CAP) are prone to develop complications such as myocardial infarction, cardiac arrhythmias, and congestive heart failure[1-3]. All of these adverse cardiovascular events pose a risk for both short-term and long-term mortality[3, 4]. In this context, several risk factors have been described, most importantly advanced age, pre-existing cardiovascular morbidity and acute pneumonia severity [5, 6]. However, one cardiac complication that has received far less attention is the occurrence of 'silent' myocardial injury. A handful of reports have shown that CAP can be associated with high plasma cardiac troponin levels without symptoms of myocardial infarction[7], and that these elevations are related to increased mortality[8, 9]. Unfortunately, most studies have relied on cardiac troponin measurements that were ordered on clinical indication (introducing information bias) or solely performed upon intensive care unit (ICU) admission (limiting temporal resolution)[7-9]. As a result, there is currently a lack of knowledge regarding the true incidence of myocardial injury as well as the dynamics of cardiac troponin release over time. Likewise, only limited information is available about risk factors for troponin release, as most previous studies have focused on baseline predictors and were unable to assess whether and when a rise or fall in troponin occurred[7-9]. With the current study we aimed to provide a more detailed description of the clinical settings during which troponin release occurs in patients admitted to the ICU with severe CAP in order to identify (1) patient-level risk factors for the development of myocardial injury, and (2) time-dependent risk factors affecting the daily rise and/or fall of troponin levels during ICU stay.

Methods

Study design

This study was part of the Molecular Diagnosis and Risk Stratification of Sepsis project, an observational cohort study in the mixed ICUs of two tertiary centers in The Netherlands. The institutional review boards of both hospitals approved an opt-out method for obtaining consent and approved the current study (protocol numbers 10-056C and 15-232). We included consecutive patients with severe CAP admitted between January 2011 and May 2015. The post-hoc likelihood of infection had to be rated at least probable according to strict criteria, as previously described in detail [10]. In summary, all patients required both a high clinical suspicion of pneumonia and clear radiographic evidence of new or progressive pulmonary consolidations. Patients were excluded if the clinical onset of pneumonia had occurred more than 48 hours before ICU admission. We also excluded patients following cardiopulmonary resuscitation prior to ICU admission, patients not meeting organ failure criteria as described in detail previously[11], and patients who had been transferred from other hospitals.

Data collection

We identified potential risk factors of troponin release through a search of the literature[3, 5, 6, 12-22] and classified them according the following clusters: (A) patient-level risk factors present at baseline, and (B) three categories of time-dependent risk factors: (1) markers of inflammation and coagulation, (2) determinants of myocardial oxygen supply-demand mismatch, and (3) other potential causes of troponin release. All patient-level and most time-dependent risk factors had been prospectively recorded within the MARS study, yet some required additional retrospective review of the medical chart in order to yield accurate classifications. A complete list of all risk factors studied and their definitions can be found in table S1 (supplementary material). Additionally, in the event that troponin release had

been clinically recognized, we recorded the results of cardiac diagnostic procedures (such as ECG and echocardiography) and any therapeutic interventions that were subsequently initiated.

Troponin measurements and outcome definitions

We measured high-sensitivity cardiac troponin I (hs-cTnI) in heparinized plasma samples collected daily during the first week in ICU (Abbott ARCHITECT STAT High Sensitive Troponin-I, Abbott Diagnostics, Chicago, IL, USA). The upper reference limit for the hs-cTnI assay was 26 ng/L [23]. Patients with no available plasma samples were excluded. All observation days during the first week in ICU were classified into one of the following three categories: (1) *no troponin release*, (2) *possible troponin release*, or (3) *definite troponin release*. An ICU day was categorized as *no troponin release* if it was followed by a hs-cTnI concentration constituting both an absolute decrease of > 26 ng/L and a relative decrease >40% from a prior measurement, or any value below the upper reference limit of 26 ng/L. An ICU day was categorized as *definite troponin release* if it was followed by a value constituting both an absolute hs-cTnI increase of >26 ng/L and relative increase of >40%. All days not fulfilling these definitions were categorized as *possible troponin release*. In addition, patients were grouped according to release pattern, based on a visual inspection of troponin trajectories.

Statistical analysis

We fitted multivariable models in order to assess (1) the association between baseline risk factors and hs-cTnI concentrations on ICU admission, and (2) the relation between time-dependent risk factors and daily changes in hs-cTnI concentrations during the first week of ICU stay. For model one we used linear regression analysis, with hs-cTnI measured on day 1 as the dependent variable, and with all baseline risk factors as covariates. For model two we used linear mixed-effects regression analysis, with hs-cTnI

concentration on day X+1 as the dependent variable conditional on the hs-cTnI value on day X, thereby effectively modelling daily changes in troponin. A random intercept was included to account for the correlation between repeated measurements. As covariates, the model initially included all risk factors in table S1 (Supplementary material). However, we subsequently excluded variables showing evidence of multicollinearity or having a very low observed incidence (≤1%). To facilitate interpretation of the models, all beta-coefficients are expressed on a scale that reflects the percentage change in hs-cTnI level on subsequent days (with corresponding 95% confidence interval) per unit increase in each predictor variable. Missing data were handled by multiple imputation. Details on the multivariable models, study definitions, and imputation procedure can be found in the additional file (Supplementary material: supplemental methods). Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) or R version 3.2.2 (R Foundation for Statistical Computing, 2015).

Results

Among 388 consecutive CAP patients treated during the years of enrolment, 200 were eligible for study inclusion (figure 1). A total of 20 subjects were excluded because of missing plasma samples and one patient because electronic health records were unavailable due to technical issues, leaving 179 (90%) patients with a total of 792 observation days during the first week in ICU for analysis. Upon first presentation to the ICU, hs-cTnI levels >26 ng/L were observed in 130 (73%) subjects. An additional 22 (12%) patients who entered the ICU having normal troponin values demonstrated troponin release during subsequent days in ICU. Overall, elevated troponin levels were observed on 499 (63%) of the 792 ICU days studied.

Troponin release patterns

A total of 152 patients (ever) had troponin release during their first week in ICU, with 148 (97%) elevations occurring within the first 4 days. Maximum plasma concentrations were observed on day 1 in 78 (51%) of these cases, and 124 (82%) of subjects reached their peak before day 4. Figure 2 shows hs-cTnI levels for patients having various temporal release patterns. Patients with declining patterns were older with similar disease severity, yet had a lower 30-day mortality compared to the rest of the patients, suggesting that early decreasing troponin concentrations may convey favorable prognostic information in patients with CAP (Supplementary material: table S2).

Clinical management of troponin release

Among the 152 patients with troponin release, only a minority of 45 (30%) subjects had their troponin measured by the treating physicians and were thus clinically recognized. Further diagnostic tests that were subsequently ordered included echocardiography in 19 (42%) and full 12-lead ECG in 29 (64%) subjects, with the latter revealing signs of myocardial ischemia in 16 (55%) cases. Clinical management

usually amounted to a 'wait and see' policy, consisting of successive troponin measurements and clinical monitoring. In 19 of the 45 patients (42%) with clinically recognized myocardial injury a cardiologist was consulted, and antiplatelet or anticoagulant therapy was initiated in 9 subjects (20%).

Patient-level (baseline) risk factors for troponin release

Patients with elevated hs-cTnI plasma concentrations on admission were older and more frequently had a history of coronary artery and peripheral vascular disease than those with normal hs-cTnI levels (table 1). In addition, patients with myocardial injury had higher acute physiology and chronic health evaluation (APACHE) IV scores (indicating greater disease severity), yet their 30-day mortality rate was not different.

Figure 3 shows the results of the multivariable linear model. After adjustment the following risk factors remained independently associated with increased hs-cTnI levels upon ICU admission: coronary artery disease (160% increase, 95% CI 7-529, p-value 0.03), smoking (304% increase, 95% CI 59-924, p-value 0.003), and higher APACHE IV scores (2% increase, 95% CI 0.7-3.3, p-value 0.002). The presence of *S. aureus* as causative pathogen was associated with reduced hs-cTnI levels on ICU admission compared to other pathogens (67% reduction, 95% CI 9-88, p-value 0.03).

Time-dependent (daily) risk factors for troponin release

Crude comparisons revealed lower platelet counts and prolonged prothrombin times on the days when troponin release occurred, suggesting an increased activation of the coagulation system (table 2). In addition, we observed more hypotension, shock, a greater use of catecholamines, and anemia on such days, suggesting a myocardial oxygen supply-demand mismatch. The incidence of alternative (non sepsis-related) diagnoses that may explain troponin release, such as stroke, peri-/myocarditis,

rhabdomyolysis, pulmonary hypertension, circulatory arrest, and cardiac contusion, was low. However, acute kidney injury was more prevalent on days with troponin release, whereas the use of antiplatelet drugs and macrolide antibiotics seemed to protect against this.

Figure 4 shows the results of the mixed-effects model. After multivariable adjustment several risk factors remained independently associated with higher hs-cTnI levels on the next ICU day, including tachycardia (1.6% increase, 95% CI 0.3-3, p-value 0.02), hypotension (5.1% increase, 95% CI 1-9.4, p-value 0.01), use of dobutamine (38.4% increase, 95% CI 8.8-76, p-value 0.008) and lower platelet count (1.7% increase per unit decrease, 95% CI 0.1-3.4, p-value 0.04). No variables from the cluster of other factors remained significantly associated with hs-cTnI.

Discussion

We systematically measured daily plasma concentrations of troponin during a week following onset of severe CAP and observed evidence of myocardial injury in a large majority (85%) of patients. Almost all cases of troponin release became evident within the first 4 days. Patient characteristics associated with troponin release at ICU admission included smoking and coronary artery disease, whereas *Staphylococcus aureus* as a primary causative pathogen of pneumonia seemed to protect against this. More importantly, an analysis of time-dependent factors associated with the daily rise and fall of troponin levels pointed towards activated coagulation and myocardial oxygen supply-demand mismatch as the most likely causes of myocardial injury.

Previous studies in CAP patients have reported apparent incidences of troponin release between 19% and 58%[8, 9, 24], which is considerably lower than what we observed. However, most of these studies did not systematically measure plasma concentrations on a daily basis, used less sensitive troponin assays, and included patients with lower severity of disease than we did. The 85% incidence of myocardial injury observed in our study is very similar to rates previously reported by studies that methodically applied troponin screening in patients with severe sepsis (85%) and general critical illness (84%)[25, 26].

Baseline variables that have previously been identified as possible risk factors for troponin release in CAP patients include advanced age, high disease severity, renal dysfunction, ischemic heart disease, smoking, and the presence of chronic obstructive pulmonary disease, peripheral artery disease, and diabetes[8, 9, 24]. Among these, only a history of coronary artery disease, smoking, and acute disease severity (APACHE) could be confirmed in our study. This might be explained by the fact that many studies did not perform multivariable adjustment[8, 9, 24], or were conducted in a clinical domain that

predominately included non-ICU patients[8, 24]. The observed protective effect of *Staphylococcus aureus* on hs-cTnI levels represents a novel finding and requires confirmation in future studies.

We are not aware of studies that have investigated time-dependent predictors of cardiac troponin release. In the present study we found that tachycardia, hypotension, dobutamine use, and low platelet counts were associated with increasing hs-cTnI plasma concentrations. This suggests that myocardial oxygen supply-demand mismatch, and possibly an activated coagulation system, are the principal drivers of troponin release during sepsis. The fact that type 2 myocardial ischemia (i.e., related to supply-demand mismatch) rather than type 1 infarction (i.e., related to a primary coronary event) should be held responsible for myocardial damage in this setting is supported by observations in patients admitted to the ICU with the systemic inflammatory response syndrome (SIRS) or sepsis, in whom troponin release was not associated with abnormalities on coronary angiography or stress echocardiography in the majority of cases [27]. In addition, autopsies performed in patients who succumbed to sepsis revealed no evidence of significant myocardial cell necrosis [28]. A role for activated coagulation in the pathogenesis of myocardial injury during sepsis is supported by results of a previous cohort study in less severe CAP patients, which showed that elevated concentrations of several markers of platelet activation in plasma were associated with the development of myocardial infarction [24]. In contrast, assessment of clot formation using rotational thromboelastometry yielded no differences between hs-cTnI-positive and -negative patients with SIRS, sepsis, or septic shock, although the sample size of 38 subjects provided only limited power to this study [29].

Median troponin concentrations observed in the current study were similar to those in patients diagnosed with non ST-elevation myocardial infarctions[30], indicating that CAP patients may suffer serious cardiac injury. Importantly, only 30% of troponin release events in our study were recognized by the treating ICU physicians. Furthermore, a cardiologist was consulted in less than half of these cases,

and subsequent clinical management was mostly conservative. This practice reflects our limited understanding of both the underlying etiology and prognostic implications of troponin release during sepsis. Since there are currently no well-defined treatment options, many physicians adopt a pragmatic 'wait and see' approach.

Our study has several limitations. First, we only measured hs-cTnI concentrations in plasma once daily, thereby possibly missing smaller troponin elevations. Second, we did not measure hs-cTnI until the patient arrived in the ICU. As plasma levels followed a declining trajectory in 36% of patients, it is likely that peak troponin concentrations (and any accompanying time-dependent etiologic factors) may not have been correctly detected in all subjects. Third, because of the strict observational nature of our study not all patients underwent a full diagnostic work-up for all possible causes of troponin elevation. However, given its multicenter design we believe that our study reflects current practice across diverse clinical settings. Finally, we used a complex mixed-effects regression model which should be regarded as exploratory given the large number of predictors for troponin release. Furthermore, the model residuals showed some evidence of non-normality, which may have resulted in increased standard errors and more conservative p-values (see supplementary material for details).

Conclusions

Myocardial injury develops in a large majority of patients with severe CAP and predominantly occurs early during its clinical course. Myocardial oxygen supply-demand mismatch and an activated coagulation system are potential causes of this injury.

Ethics approval and consent to participate

The medical ethical committees of the Academic Medical Center in Amsterdam and the University Medical Center in Utrecht approved an opt-out method for obtaining consent and approved the current study (protocolnumbers 10-056C/15-232).

Conflicts of interest

The authors declare that they have no competing interests

Funding

This study is supported by the Center for Translational Molecular Medicine (http://www.ctmm.nl), MARS project (Grant 04I-201).

Contributions

JFF, LvB, THK, DWD, JH, TvdP, WvK, MJMB, and OLC substantially contributed to the conception and design of the study. JFF and LvB acquired the data. JFF and LvB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JFF, LvB, THK, WvK, MJMB, and OLC were involved in the interpretation of the data. JFF and OLC drafted the manuscript and all authors revised it critically for important intellectual content. All authors gave final approval of this version to be submitted.

Acknowledgements

We thank all members of the MARS consortium and trial nurses for their participation in the data collection. We thank Ron Stokwielder and Tesy Merkx for their assistance in laboratory measurements. In addition we thank Linda M. Peelen for her invaluable help in data analysis.

MARS consortium

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Table 1. Patient characteristics stratified by troponin plasma concentration at ICU admission (n=179)

Variable	**Admission hs-cTnI ≤26 ng/L (N=49)**	**Admission hs-cTnI >26 ng/L (N=130)**	**p-value**
Age (years)	61 (48-68)	65 (50-74)	0.04
Gender (males)	29 (59%)	84 (65%)	0.50
BMI (kg/m^2)	26 (23-29)	24 (22-27)	0.06
Comorbidity			
Coronary artery disease	4 (8%)	31 (24%)	0.02
Cerebrovascular disease	5 (10%)	20 (15%)	0.37
Chronic renal insufficiency	4 (8%)	16 (12%)	0.43
Congestive heart failure	3 (6%)	10 (8%)	0.72
Diabetes mellitus	11 (22%)	27 (21%)	0.81
Hypertension	14 (29%)	40 (31%)	0.78
Peripheral vascular disease	2 (4%)	25 (19%)	0.01
Myocardial infarction	4 (8%)	15 (12%)	0.51
COPD	9 (18%)	31 (24%)	0.43
Active smoker	6 (12%)	19 (15%)	0.68
Causative pathogen			
Streptococcus pneumoniae	9 (18%)	29 (22%)	0.57
Staphylococcus aureus	11 (22%)	11 (8%)	0.01
ICU admission characteristics			
Mechanical ventilation	47 (96%)	117 (90%)	0.20
APACHE IV Score	75 (64-89)	86 (71-109)	0.001
ICU length of stay (days)	7 (3-14)	8 (4-15)	0.61
ICU mortality	9 (18%)	32 (25%)	0.38
30-day mortality	15 (31%)	41 (32%)	0.91

Data are presented as absolute number (%) or median (Q1-Q3).

ICU intensive care unit, *hs-cTnI* high-sensitivity cardiac troponin I, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *APACHE* acute physiology and chronic health evaluation.

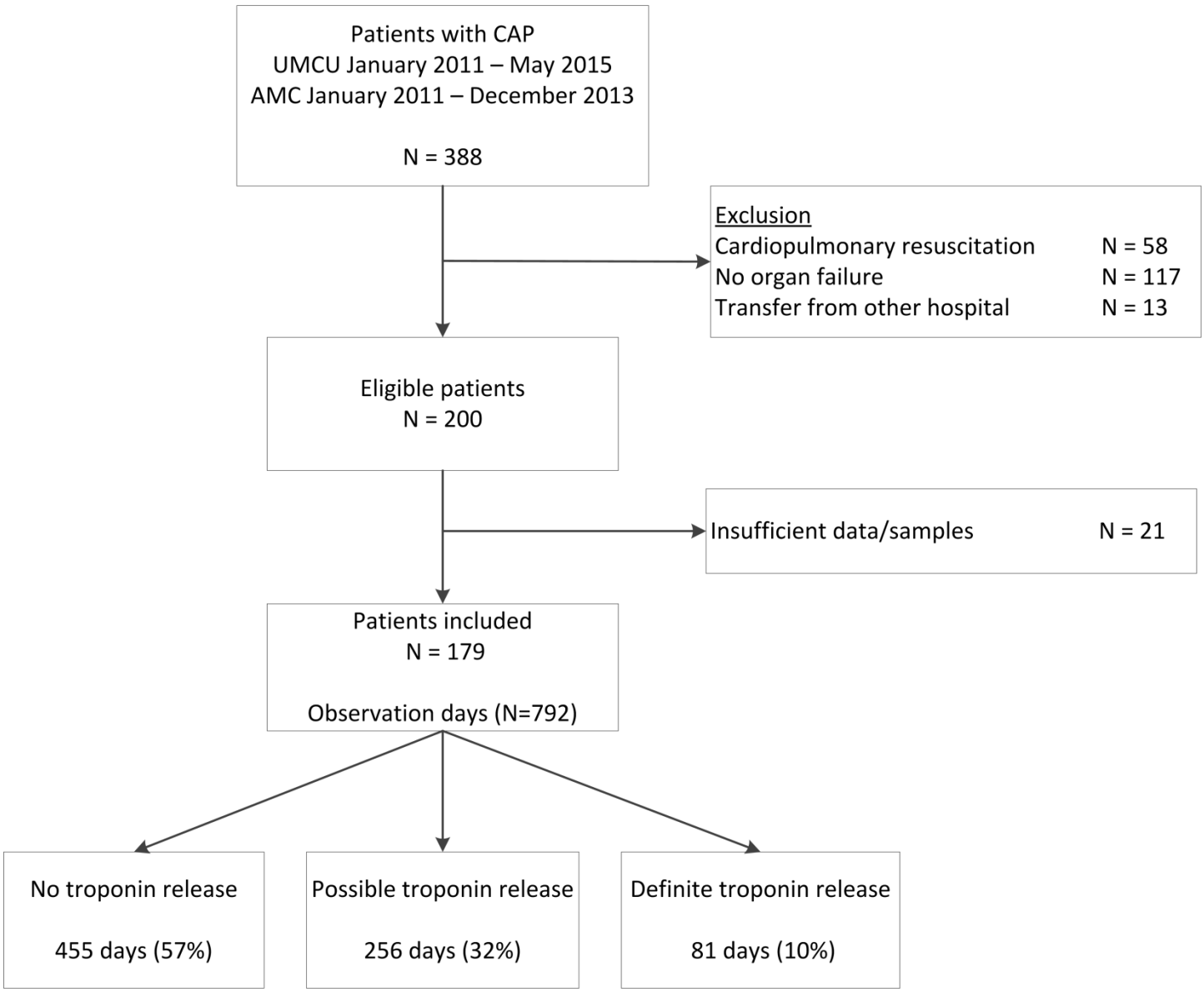
Table 2. Characteristics of ICU days for different categories of troponin release (n=792)

Variable	No troponin release (N=455)	Possible troponin release (N=256)	Definite troponin release (N=81)	p-value for trend*
Inflammation/coagulation factors				
C-reactive protein (mg/L)	153 (77-249)	152 (71-245)	169 (62-273)	0.91
White blood cell count (10^9/L)	12.4 (8.4-16.8)	12.9 (8.4-19.0)	13.6 (8.7, 18.7)	0.42
Fever (>38.5 °C)	56 (12%)	30 (12%)	19 (23%)	0.06
Prothrombin time (s)	14.6 (12.9-16.4)	15.3 (13.7-18.4)	15.8 (13.9-18.9)	0.003
Platelet count (10^9/L)	182 (106-253)	149 (79-222)	143 (69-216)	<0.001
Supply/demand factors				
Tachycardia (hours HR >120 beats/min)	0 (0-1)	0 (0-0)	0 (0-3)	0.14
Hypotension (hours MAP <60 mm Hg)	0 (0-0)	0 (0-1)	0 (0-1)	<0.001
Shock index (hours HR/SBP >1)	0 (0-6.0)	0 (0-6.0)	4 (0-11)	0.004
Norepinephrine use	233 (51%)	139 (54%)	45 (56%)	0.63
Norepinephrine dose (ng/kg/min)	92 (51-167)	112 (60-215)	143 (65-365)	<0.001
Dobutamine use	32 (7%)	26 (10%)	13 (16%)	0.007
Dobutamine dose (ug/kg/min)	3.3 (2.1-4.5)	3.6 (2.7-4.9)	3.7 (1.9-4.7)	0.87
Severe anemia	61 (13%)	59 (23%)	16 (20%)	0.007
Other factors				
Acute kidney injury	133 (29%)	109 (43%)	37 (46%)	<0.001
Respiratory failure	297 (65%)	176 (69%)	61 (75%)	0.07
Acute stroke	8 (2%)	6 (2%)	4 (5%)	0.21
Cardiotoxic cancer drugs	18 (4%)	17 (7%)	8 (10%)	0.06
Acute heart failure	63 (14%)	31 (12%)	10 (12%)	0.79
Acute peri-/myocarditis	3 (1%)	2 (1%)	1 (1%)	0.86
Acute rhabdomyolysis	13 (3%)	11 (4%)	2 (2%)	0.53
Acute pulmonary hypertension	0 (0%)	0 (0%)	1 (1%)	n.a.
Circulatory arrest	0 (0%)	0 (0%)	1 (1%)	n.a.
Cardiac contusion	0 (0%)	0 (0%)	2 (2%)	n.a.
Macrolide use	113 (25%)	43 (17%)	13(16%)	0.009
Antiplatelet drug use	124 (27%)	67 (26%)	8 (10%)	0.007
Beta-blocker use	30 (7%)	21 (8%)	8 (10%)	0.50
Statin use	107 (24%)	60 (23%)	19 (23%)	0.99

Data are presented as median (Q1-Q3) or absolute number (%). * Cochran-Armitage trend test was used for dichotomous variables and linear regression for continuous variables (only if a one-way ANOVA or kruskal-wallis test revealed a significant difference between groups).

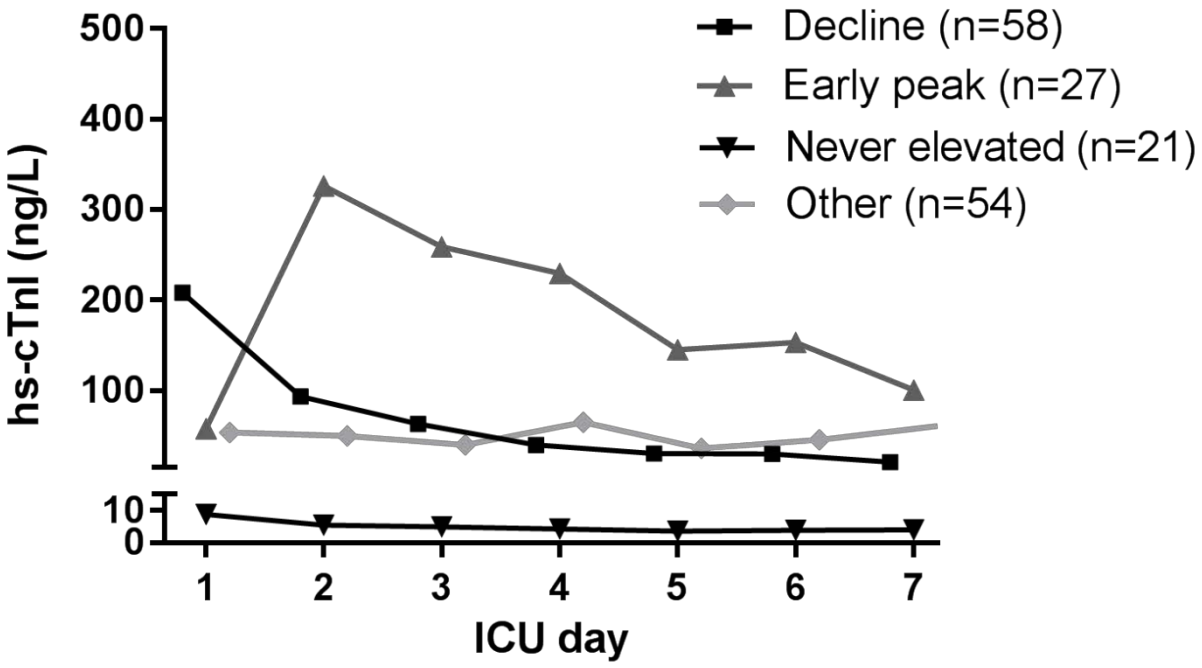
ICU intensive care unit, *HR* heart rate, *MAP* mean arterial pressure, *SBP* systolic blood pressure, *n.a.* not applicable.

Figure 1. Patient inclusion flow chart



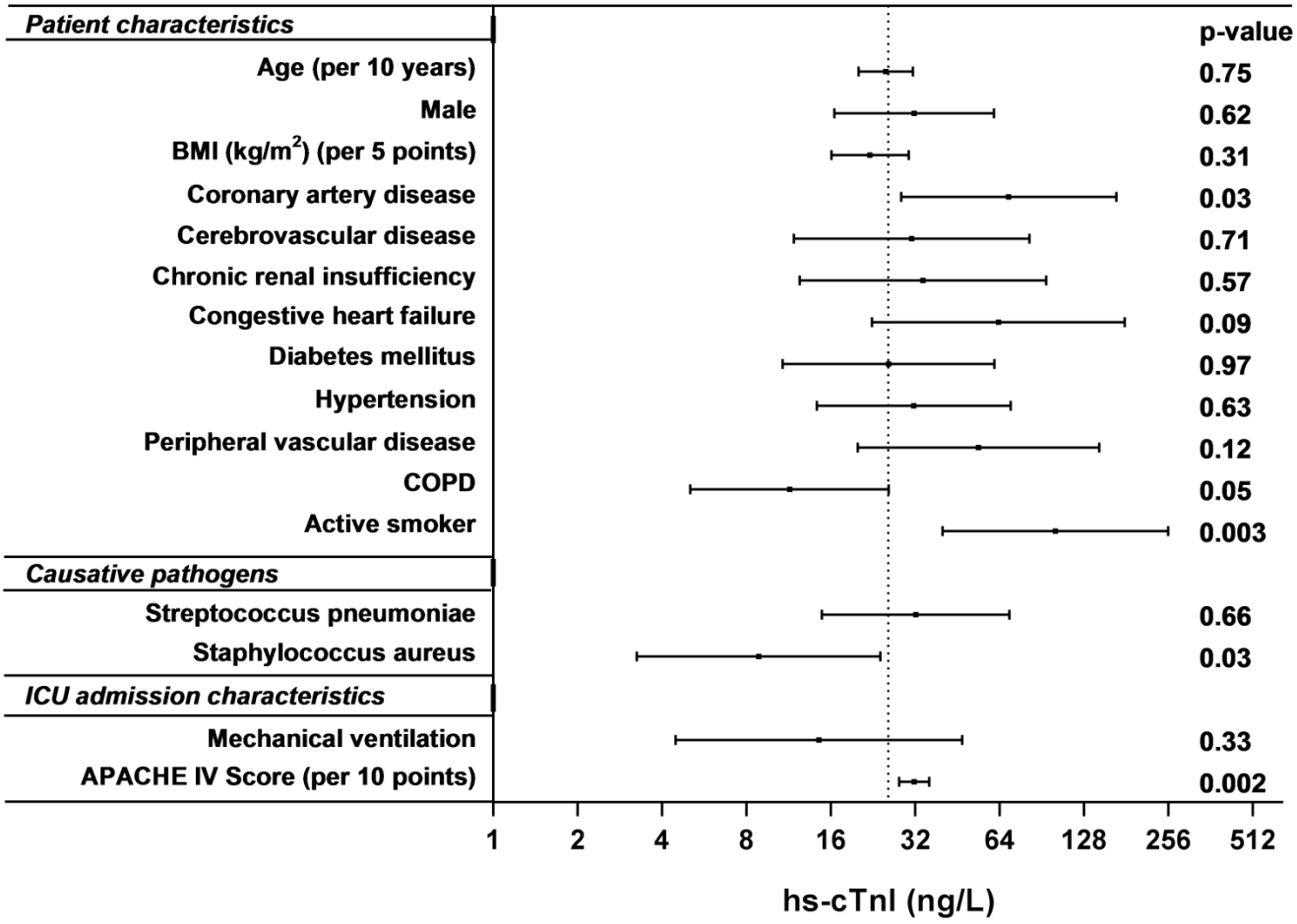
CAP Community-acquired pneumonia, *UMCU* University Medical Center Utrecht, *AMC* Academic Medical Center.

Figure 2. Median troponin plasma concentrations of hs-cTnI during the first 7 days in the ICU (n=160)



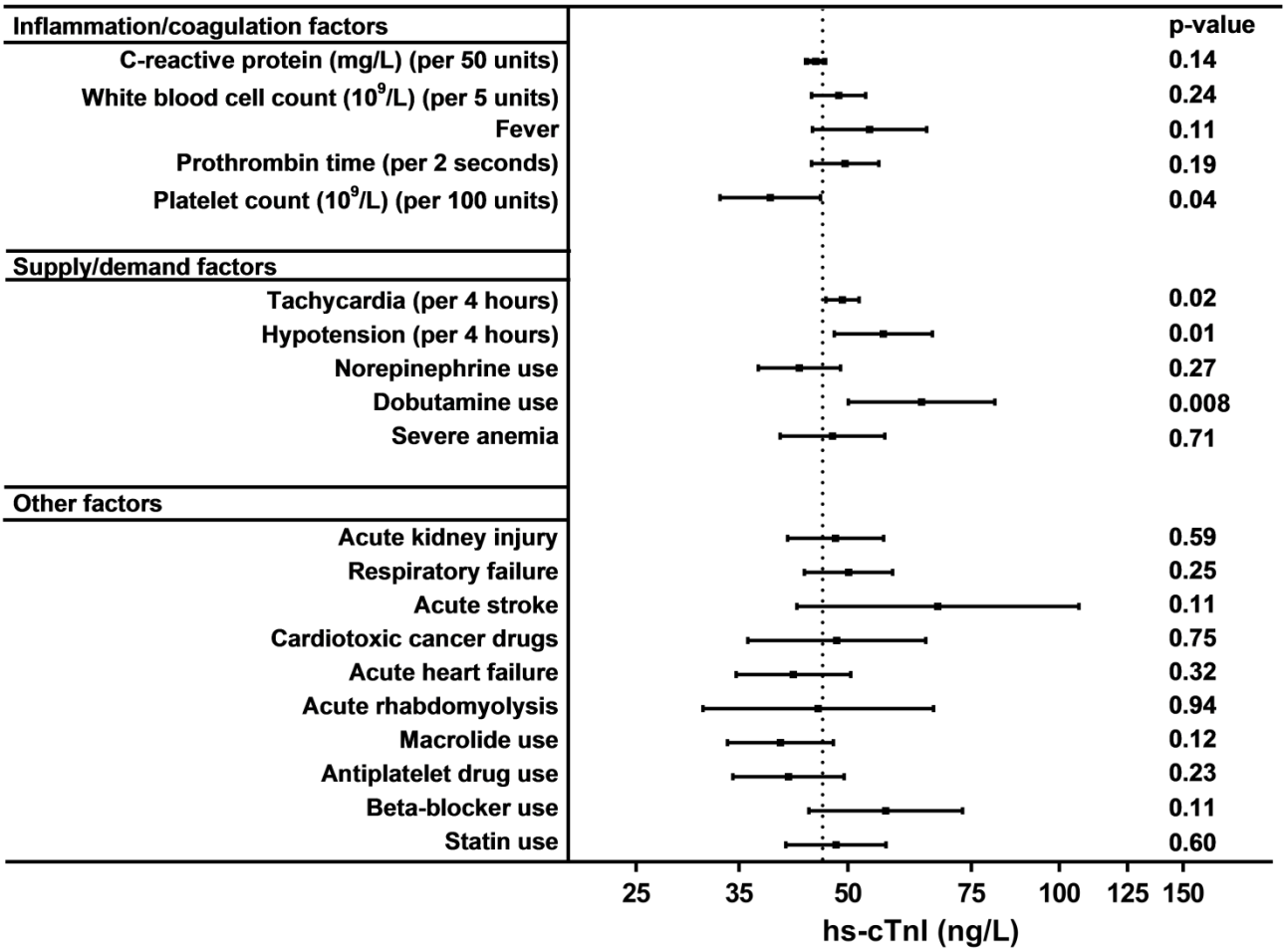
Troponin trajectories were categorized based on a visual inspection of serial hs-cTnI concentrations in plasma; 19 patients in whom only a single hs-cTnI measurement was performed (on day 1) were excluded. *hs-cTnI* High-sensitivity cardiac troponin I, *ICU* intensive care unit.

Figure 3. Results of a multivariable linear regression model exploring associations between patient-level (baseline) risk factors and troponin plasma concentrations on ICU admission (n=179 patients).



The vertical dotted line shows the expected hs-cTnI concentration when all risk factors are set to zero (i.e., this represents the intercept of the multivariable linear model). The horizontal bars represent the predicted hs-cTnI concentration (with 95% CI) in the presence of the risk factor. The full regression model is depicted in table S3 (Supplementary material). *ICU* intensive care unit, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *APACHE* acute physiology and chronic health evaluation, *hs-cTnI* high sensitivity cardiac troponin I.

Figure 4. Results of multivariable mixed-effects regression model assessing the influence of time-dependent risk factors on daily hs-cTnI plasma concentrations during the first week in ICU (n=792 observation days).



The vertical dotted line shows the median hs-cTnI concentration of all ICU days. The horizontal bars represent the predicted hs-cTnI concentration (with 95% CI) on the next ICU day in the presence of the time-dependent risk factor. The full regression model (including baseline covariates such as age and comorbidities) is depicted in table S4 (Supplementary material). *hs-cTnI* high sensitivity cardiac troponin I, *ICU* intensive care unit.