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ORIGINAL ARTICLE

High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia

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ABSTRACT

Background and objective: **Mortality after hospitalization with community-acquired pneumonia (CAP) is high, compared with age-matched controls. Available evidence suggests a strong link with cardiovascular disease. Our aim was to explore the prognostic value of high-sensitivity cardiac troponin T (cTnT) for mortality in patients hospitalized with CAP.**

Methods: **CTnT level on admission was measured (assay conducted in 2015) in 295 patients hospitalized with CAP who participated in a randomized placebo-controlled double-blind trial on adjunctive dexamethasone treatment. Outcome measures were short- (30-day) and long-term (4.1-year) mortalities.**

Results: **CTnT levels were elevated (≥14 ng/L) in 132 patients (45%). Pneumonia severity index (PSI) class was 4–5 in 137 patients (46%). Short- and long-term mortality were significantly higher in patients with elevated cTnT levels. cTnT level on admission combined with PSI classification was significantly better in predicting short-term mortality (area under the operating curve (AUC) = 0.903; 95% CI = 0.847–0.960), compared with PSI classification alone (AUC = 0.818; 95% CI = 0.717–0.919). An optimal cTnT cut-off level of 28 ng/L was independently associated with both short- and long-term mortality (OR = 21.9; 95% CI = 4.7–101.4 and 10.7; 95% CI = 5.0–22.8, respectively).**

Conclusion: **Elevated cTnT level on admission is a strong predictor of short- and long-term mortalities in patients hospitalized with CAP.**

Key words: biomarkers, cardiovascular system, mortality, pneumonia, troponin T.

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SUMMARY AT A GLANCE

High mortality rates after hospitalization with community-acquired pneumonia (CAP) have been associated with cardiovascular disease. In a well-described cohort, we demonstrated that cardiac troponin T on admission with CAP is a strong independent predictor of short- and long-term mortality, possibly reflecting acute cardiac damage or disease severity.

Abbreviations: ACS, acute coronary syndrome; ASA, aspirin; AUC, area under the operating curve; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; cTnT, cardiac troponin T; CURB-65, confusion, urea, respiratory rate, blood pressure and 65 years of age; ECG, electrocardiogram; ICU, intensive care unit; IQR, interquartile range; PSI, pneumonia severity index; ROC, receiver operating curve; WBC, white blood cell.

INTRODUCTION

It has been shown that both short- and long-term mortality are high after hospitalization with community-acquired pneumonia (CAP), compared with age-matched controls.[1–3] Exact mechanisms explaining the high mortality in CAP survivors have not yet been elucidated. A strong association with cardiovascular disease has, however, been suggested.[4,5] This theory is supported by an increased rate of cardiac complications after an episode of CAP.[6] Inflammation-induced platelet activation may play an important role in the acute phase of pneumonia, linking inflammation and cardiovascular disease.[7,8]

Pneumonia severity index (PSI) and CURB-65 (acronym for confusion, urea, respiratory rate, blood pressure and 65 years of age) are clinical scoring systems which predict mortality in patients with CAP.[9,10] To further increase the predictive value of these models,

biomarkers in CAP have been subject of study, including cardiac biomarkers.[11–13] For example, a recent prospective study assessed the relationship between cardiac troponin T (cTnT) elevation and in vivo markers of platelet activation in acute CAP. In this study, cTnT was elevated in 144 out of 278 (52%) of patients, of whom 31 (22%) had at least one additional criterium of myocardial infarction. In 78% of patients, cTnT elevation was isolated. Markers of platelet activation were significantly higher in patients with myocardial infarction.[14] In sepsis, it also has been shown that elevated cardiac troponin levels, measured shortly after admission, are associated with mortality.[15,16] It is unclear whether cTnT elevation during CAP is a reflection of myocyte damage, possibly due a temporary oxygen demand/supply mismatch or of underlying coronary artery disease.[17]

The aim of this post hoc analysis was to explore the prognostic value of high-sensitivity cTnT for mortality in hospitalized patients with CAP. We hypothesized that the cTnT level at the time of hospital admission predicts mortality in patients admitted with CAP.

METHODS

Participants

Adult patients hospitalized with CAP who participated in a prior randomized double-blinded, placebo-controlled trial (NCT00471640) were included. Only patients of whom serum from time of admission was available were enrolled in this study.

The trial was conducted between November 2007 and September 2010. It was primarily designed to assess the effect of adjunctive dexamethasone treatment on length of hospital stay in adult patients with CAP. Secondary end points included in-hospital and 30-day mortality, intensive care unit (ICU) admission and hospital readmission. Patients were enrolled in the St. Antonius Hospital in Nieuwegein or the Gelderse Vallei Hospital in Ede, <24 h after initial presentation at the emergency department. Inclusion and exclusion criteria from the original study are described in detail elsewhere.[18] Important exclusion criteria were an immunocompromised state, administration of chemotherapy or corticosteroids within the last 6 weeks or an indication for systemic corticosteroid therapy.

On admission, co-morbidities were registered and baseline PSI score was calculated. Long-term survival status was collected by contacting patients' general practitioners and information was verified by checking hospital records using business intelligence software. Maximum follow-up duration ranged from 4.1 to 6.9 years. We used 4.1 years for our long-term analyses. Antiplatelet therapy usage was collected from hospital pharmacist's files and patients' medical records. It was defined as current use of a platelet aggregation inhibitor on admission and prescription in the last six consecutive months prior to admission. Proof of symptoms indicating cardiac complication (chest pain, novel arrhythmia, signs of heart failure or novel ECG abnormalities) was collected from patients' medical charts. All patients gave informed consent and ethical approvals were obtained from the Medical Ethical Committee of the St. Antonius Hospital.

High-sensitivity cTnT measurement

Blood samples were obtained and deep frozen (–80°C/–112°F) directly after initial collection on day of admission. Serum levels were determined in all blood samples using fifth generation high-sensitivity cTNT (Cobas 6000, Roche Diagnostics, Basel, Switzerland) assays, in accordance with the manufacturer's instructions. The assay was conducted in 2015. The 99th percentile upper reference limit of this high-sensitivity assay was determined at 14 ng/L, based on manufacturer's guidelines.[19] Values ≥14 ng/L were considered to be elevated.

Statistical analysis

Descriptives were stated as number (%) and continuous data were presented as mean (SD) or median (interquartile range (IQR)). Area under the receiver operating characteristics curve analysis was used to determine the cTnT cut-off level on admission with the highest combined sensitivity and specificity, using 30-day mortality as state variable. Values above this cut-off level will hereafter be named 'high'. Baseline differences between patients, based on admission cTnT level, were tested with an independent sample t-test, chi-square test or Mann–Whitney U-test, where appropriate. Patients were categorized into three baseline groups based on the cTnT upper reference level and the determined optimal cut-off level for mortality prediction. Because multiple comparisons were made to evaluate baseline differences, a *P*-value <0.001 was applied in Table 1. Crude survival of patients with different cTnT cut-off levels on admission was calculated using Kaplan–Meier analyses with a log-rank test.

Multivariable logistic regression analyses were applied to study the association between cTnT level on admission and 30-day and long-term mortalities. Potential confounding variables were selected for inclusion in the model based on rational judgment. For statistical reasons (no deaths occurred in patients with PSI class 1), PSI was categorized as 1–3 and 4–5 for regression analyses. Possible outcome predictors included in the PSI were not simultaneously included in the multivariable model. An interaction between current antiplatelet therapy and high cTnT on admission could be expected and was tested statistically.

By comparing areas under the operating curve (AUC), the potential of cTnT and PSI prognostication (both separately and combined) was compared. To assess the discriminative ability of the final model, we performed receiver operating curve (ROC) analysis.

Data analysis was performed using IBM SPSS statistics, version 22, for Windows (IBM Corp, Armonk, NY, USA). A two-tailed *P*-value of <0.05 or <0.001 (where appropriate) was considered significant. All figures were created using Prism software (GraphPad Corp., San Diego, CA, USA).

Table 1 Baseline characteristics and outcomes of the 295 patients hospitalized with community-acquired pneumonia, based on cTnT level on admission

Baseline	All patients (n = 295)	cTnT < 14 ng/L (n = 163)	cTnT = 14–28 ng/L (n = 64)	cTnT > 28 ng/L (n = 68)
Male sex	167 (56.6)	83 (50.9)†	45 (70.3)	39 (57.4)
Age in years	63.6 (18.3)	54.8 (17.1)††	72.8 (11.7)	76.1 (14.0)‡‡
Caucasian ethnicity	286 (96.9)	160 (98.2)	63 (98.4)	63 (98.4)
Nursing home	16 (5.4)	4 (2.5)	3 (4.7)	9 (14.3)‡
Smoking¶	80 (27.1)	65 (43.3)†	9 (15.5)	6 (9.7)‡‡
Co-morbidities				
Chronic renal failure	27 (9.2)	2 (1.2)†	6 (9.4)§	19 (27.9)‡‡
Diabetes mellitus	42 (14.2)	17 (10.4)	9 (14.1)	16 (23.5)‡
Liver disease	2 (0.7)	0	1 (1.6)	1 (1.5)
Neoplastic disease	19 (6.4)	4 (2.5)†	9 (14.1)	6 (9.4)‡
Chronic heart failure	49 (16.6)	10 (6.1)†	14 (21.9)	25 (15.2)‡
PSI class				
Classes 1–3	158 (53.6)	124 (76.1)††	16 (25.0)	18 (26.5)‡‡
Classes 4–5	137 (46.4)	39 (23.9)††	48 (75.0)	50 (73.5)‡‡
Blood pressure				
Systolic in mm Hg	132 (22)	130 (19)	134 (25)	133 (24)
Diastolic in mm Hg	74 (12)	76 (11)	73 (13)	72 (13)‡
Temperature in °C	38.2 (1.1)	38.2 (1.1)	38.1 (1.2)	38.0 (1.0)
Laboratory parameters				
CRP in mg/L (IQR)	217 (140)	240 (112–342)	194 (63–280)	138 (70–296)‡
WBC count ($\times 10^9$/L)	14.2 (6.5)	14.5 (6.3)	13.6 (7.2)	13.7 (6.1)
Thrombocytes ($\times 10^9$/L)	260 (103)	260 (100)	261 (127)	256 (82)
Days ill before admission (IQR)	5 (3–7)	5 (3–7)	5 (1–7)	4 (2–7)‡
Pretreated with antibiotics at home	81 (27.5)	55 (33.7)†	13 (20.3)	13 (20.3)‡
Antiplatelet therapy	76 (26.0)	28 (17.3)†	23 (35.9)	25 (37.9)‡
Dexamethasone§§	146 (49.5)	81 (49.7)	29 (45.3)	36 (52.9)

Data are presented as number (%), mean (SD) or median (IQR).
§§Dexamethasone was given as part of a clinical trial.
¶24 missings.
†Difference between groups 1 and 2, $P < 0.05$.
††Difference between groups 1 and 2, $P < 0.001$.
‡Difference between groups 1 and 3, $P < 0.05$.
‡‡Difference between groups 1 and 3, $P < 0.001$.
§Difference between groups 2 and 3, $P < 0.05$.
CRP, C-reactive protein; cTNT, cardiac troponin T; IQR, interquartile range; PSI, pneumonia severity index; SD, standard deviation; WBC, white blood cell.

RESULTS

Patients

Serum samples for cTnT measurement on admission were available for 295 out of 304 (97.0%) patients hospitalized with CAP who participated in the original trial.[18] Median age was 67 years, 56.6% of patients were males and 27.1% were active smokers. Heart failure (16.6%) was the most common co-morbidity, 9.2% had chronic renal failure. Twenty-six percent used antiplatelet therapy on admission. In 46.4% of patients, PSI class was 4–5. Median cTnT level was 12 ng/L (IQR = 6–26]. In 132 patients (44.7%), admission cTnT was elevated (≥14 ng/L).

Based on our data, the calculated optimal admission cTnT cut-off level for 30-day mortality prognostication was 28 ng/L (sensitivity = 0.88; specificity = 0.81). The prognostic value of this 'high' cut-off level will be described in a later paragraph. Baseline characteristics of patients, categorized into three groups based on cTnT level on admission (<14 ng/L vs 14–28 ng/L vs >28 ng/L), are shown in Table 1.

Patients with elevated or high cTnT levels were older and generally had more co-morbidities. Thereby, diabetes mellitus, chronic renal failure and heart failure rates were higher in patients with cTnT elevation. Compared with patients with elevated cTnT, significantly more patients with high cTnT level had chronic renal failure. In contrast, active smoking was more common in patients without elevated cTnT. Of patients with PSI 4–5, 36.5% had a high cTnT level on admission, compared with 11.4% of patients with a PSI 1–3 ($P < 0.001$).

Survival

Sixteen patients (5.4%) died during admission; five of whom had cardiac symptoms in retrospect. Fifteen of 16 patients had elevated cTnT levels on admission. Nineteen patients (6.4%) died before the planned outpatient clinic visit at day 30. Forty-nine patients (16.4%) did not survive for more than 1 year after hospital admission. The long-term (4.1 years) mortality

Table 2 Outcomes for enrolled patients based on cTnT group on admission

	All patients (n = 295)	cTnT < 14 ng/L (n = 163)	cTnT = 14–28 ng/L (n = 64)	cTnT > 28 ng/L (n = 68)
ICU admission	16 (5.4)	5 (3.1)	3 (4.7)	8 (11.8)[†]
In-hospital mortality	16 (5.4)	1 (0.6)	1 (1.6)[‡]	14 (20.6)[†]
30-Day mortality	17 (5.8)	1 (0.6)	1 (1.6)[‡]	15 (22.1)[†]
1-Year mortality	49 (16.6)	5 (3.1)[§]	8 (12.5)[‡]	36 (52.9)[†]
Long-term mortality	80 (27.1)	10 (6.1)[§]	21 (13.7)[‡]	49 (72.1)[†]

Data are presented as number (%).
[†]Difference between groups 1 and 3, $P < 0.01$.
[‡]Difference between groups 2 and 3, $P < 0.01$.
[§]Difference between groups 1 and 2, $P < 0.01$.
cTNT, cardiac troponin T; ICU, intensive care unit.

rate for all-cause mortality was 32%. Differences in ICU admission and mortality rates are shown in Table 2.

Crude survival based on cTnT cut-off level is shown in Figure 1. In the current study, crude survival did not differ between the dexamethasone and placebo group. In patients with cTnT <14 ng/L, long-term mortality was significantly higher in current antiplatelet therapy users, compared with those not on antiplatelet therapy (Fig. S1, Supplementary Information). Similar trends (but no statistical significant differences) were found when comparing survival, based on antiplatelet therapy use, between the two other baseline groups.

Prognostic value of cTnT on admission

Logistic regression analysis of our data shows that high cTnT on admission is a significant predictor of both 30-day and long-term mortalities (Table 3).

Besides cTnT, no variable was significantly associated with 30-day mortality. Active smoking was associated with a reduced chance of long-term mortality. No significant interaction between antiplatelet therapy and cTnT for predicting long-term mortality could be identified ($\beta = -0.95$, $P = 0.2$ for the interaction term high cTnT × antiplatelet therapy).

ROCs of cTnT level on admission and PSI class with corresponding AUCs for 30-day and long-term mortalities are shown in Figures 2 and 3. The combined model using cTnT and PSI was significantly better in predicting 30-day mortality, compared with using PSI alone (Fig. 2). For long-term mortality prognostication (Fig. 3), the combined model (AUC = 0.904; 95% CI = 0.868–0.940) was significantly better than both PSI classification (AUC = 0.829; 95% CI = 0.781–0.877) or cTnT alone (AUC = 0.843; 95% CI = 0.790–0.896).

DISCUSSION

CTnT elevation on admission with CAP is common and is a strong independent predictor of short- and long-term mortality. The prevalence of elevated cTnT (45%

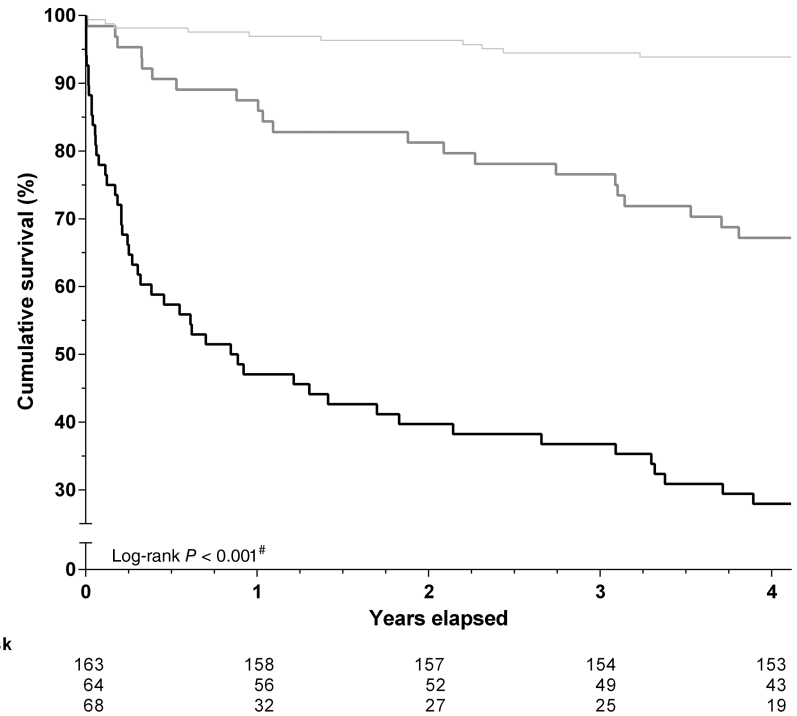

Figure 1 Crude survival based on cardiac troponin T (cTnT) level on admission. cTnT is categorized into three groups (——, cTnT < 14 ng/L; ——, cTnT = 14–28 ng/L; ——, cTnT > 28 ng/L) based on admission level (as in Table 1). #Difference between every group.

Table 3 Association between high cTnT level on admission and mortality

	30-Day mortality		Long-term mortality	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
cTnT ng/L (≤/>28)	21.9 (4.7–101.4)	<0.001	10.7 (5.0–22.8)	<0.001
PSI class (1–3/4–5)	4.2 (0.9–20.2)	0.075	7.3 (3.3–16.0)	<0.001
Antiplatelet therapy (no/yes)	1.1 (0.4–3.3)	0.865	1.9 (0.9–3.9)	0.102
Smoking (no/yes)			0.4 (0.2–0.99)	0.49

CI, confidence interval; cTnT, cardiac troponin T; OR, odds ratio; PSI, pneumonia severity index.

of enrolled patients) is in accordance with prior results in CAP that showed 52% cTnT elevation within 48 h after diagnosing CAP.[14] Similar to our findings, Chang *et al.* found an association between cTnT level on admission and 30-day mortality in patients hospitalized with CAP, although these results did not remain significant after adjusting for potential confounders.[13] To the best of our knowledge, no other studies have assessed the predictive value of admission cTnT on long-term mortality in patients with CAP. In a recent study in patients with CAP, it has been shown that cardiac troponin I on admission was independently associated with in-ICU mortality (adjusted hazard ratio = 1.398; 95% CI = 1.005–1.945). All patients were primarily admitted to the ICU with severe pneumonia in the absence of acute coronary syndrome (ACS).[20]

In our data, cTnT was a stronger predictor of 30-day mortality than PSI, which is a validated 30-day mortality prediction score in patients with CAP.[21] Using AUC analyses, we demonstrated that cTnT on admission adds significant predictive value to the PSI for both 30-day and long-term mortality prognostication (Figs 2,3).

The crude analysis of our data showed that the mortality rate is significantly higher in patients with elevated cTnT levels on admission, compared with patients without cTnT elevation. The mortality rate of patients with elevated cTnT levels on admission is high, compared with a similar and well-described Dutch cohort with mild-severe CAP and is especially high compared with the population control group.[3] Even though age and co-morbidity rates were significantly higher in patients with elevated and high cTnT level in our cohort, cTnT remained a strong predictor of mortality in the multivariable analyses. Besides diabetes mellitus, all co-morbidities shown in Table 1 are part

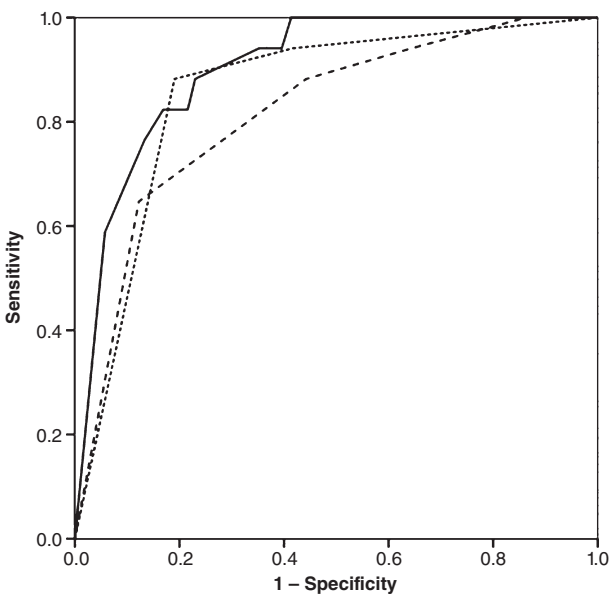

Figure 2 Operating characteristics curve of cardiac troponin T (cTnT, ·····, area under the operating curve (AUC) = 0.856; 95% confidence interval (CI) = 0.773–0.939) on admission and the pneumonia severity index (PSI, - - -, AUC = 0.818; 95% CI = 0.717–0.919) class for predicting 30-day mortality. Data on the day of admission are shown, cTnT is categorized into three groups based on admission level (as in Table 1), PSI is categorized into five classes, the final model combines the predictive value of cTnT and PSI (combined model, ——, AUC = 0.903; 95% CI = 0.847–0.960).

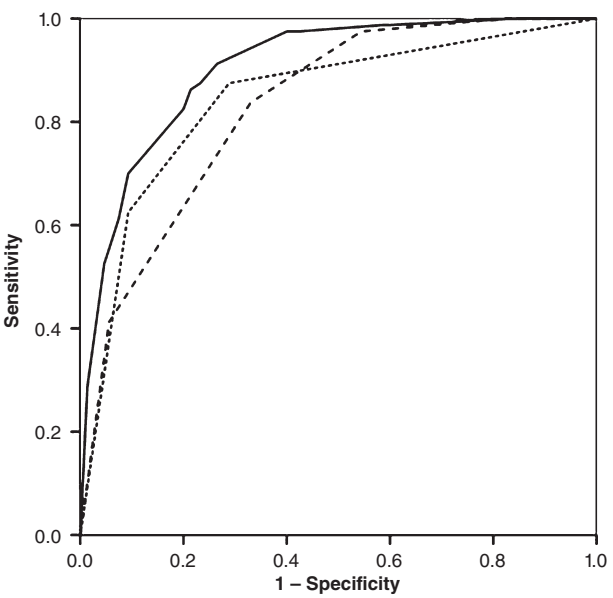

Figure 3 Operating characteristics curve of cardiac troponin T (cTnT, ·····, area under the operating curve (AUC) = 0.843; 95% confidence interval (CI) = 0.790–0.896) on admission and the pneumonia severity index (PSI, - - -, AUC = 0.829; 95% CI = 0.781–0.877) for predicting long-term mortality. Data on the day of admission are shown, cTnT is categorized into three groups based on admission level (as in Table 1), PSI is categorized into five classes, the final model combines the predictive value of cTnT and PSI (combined model, ——, AUC = 0.904; 95% CI = 0.868–0.940).

of the PSI, and were therefore not used separately in the multivariable analyses. Furthermore, neither pretreatment with antibiotics nor nursing home residency significantly influenced the model. Remarkably, cTnT elevation on admission was more common in non-smokers. This is in contrast to findings in patients with acute myocardial infarction in whom cTnT was higher in smokers, compared with non-smokers.[22] We showed that active smoking was associated with a lower long-term mortality rate in the multivariable analyses. This intriguing finding was probably the result of the exclusion of patients in need for corticosteroid therapy from the original trial. Thus, smokers who are more likely to suffer from COPD were frequently excluded from inclusion, while smokers without COPD (younger patients, less pack-years and less co-morbidity) were included. This explanation is supported by the younger age of smokers compared with non-smokers (mean = 55.2 (SD = 15.9) vs 67.2 (SD = 17.9), respectively).

CTnT is used widely as a clinical predictor of myocardial damage.[23,24] Possible mechanisms causing acute cardiac injury in patients admitted with CAP (and other infections) are oxygen supply–demand mismatch or damage due to the systemic inflammatory response which may directly influence atherosclerotic plaques and the coronary arteries.[25,26] Furthermore, in vivo platelet activation markers on admission with CAP have recently been associated with myocardial infarction during hospital stay.[14] Inflammation-induced platelet activation may link CAP to cardiovascular disease. Platelet activation potentially causes deterioration of preexisting coronary artery disease, in turn leading to ischaemia.[7,8,27] This hypothesis could explain our finding that elevated cTnT levels on admission with CAP are associated with short- and long-term mortalities. Thus, cTnT level elevation during CAP might unveil clinically unrecognized coronary artery disease and from this perspective pneumonia may be seen as a cardiac stress test.

For this reason, further studies are needed to evaluate whether diagnostic testing for cardiac injury is warranted in patients admitted with CAP with concurrent cTnT elevation. A cardiac workup, including electrocardiographic assessment and cTnT monitoring, may be warranted.[28] Second, treatment options to prevent mortality in patients admitted with CAP with high cTnT should be investigated as well.[29]

In our study, a trend for higher long-term mortality rates was seen in current antiplatelet users, compared with those not on antiplatelet therapy. This finding is probably the result of more prior recognized, and thus more severe, vascular disease in current antiplatelet therapy users on admission. Cangemi *et al.* showed that the myocardial infarction rate was not different in current aspirin (ASA) users versus non-ASA users with CAP.[14] However, initiating ASA treatment in patients hospitalized with CAP with more than one risk factor for cardiovascular disease has shown to be effective in preventing ACS up until 1 month after admission. ACS occurred in 1.1% of ASA users and in 10.6% of non-ASA users ($P = 0.015$). After 1 month, mortality was 3.3% in ASA users versus 9.6% in non-ASA users ($P = 0.151$). Thereby, a significant reduction on the risk of cardiovascular death was found.[30] Studies are needed to investigate whether initiating antiplatelet therapy in patients admitted with CAP is especially effective in case of cTnT level elevation on admission.

The most important limitation of this study is that cause of death was not reported. Therefore, we could not explore a possible relationship between cause of death and cTnT. Also, patients directly admitted to the ICU were excluded. In case of any influence, exclusion of these patients most likely resulted in underestimating the predictive value of cTnT for both short- and long-term mortality. It is unclear if performing the assay 5–8 years after collection of the blood samples has influenced cTnT levels. However, in 15 patients cTnT was measured for clinical reasons on admission and these levels were similar to those determined in the stored samples. Furthermore, reference levels have not changed since the time of initiation of the original study.

In conclusion, our findings support the hypothesis that cTnT level on admission is a predictor of 30-day and long-term mortalities in patients hospitalized with CAP.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Figure S1 Crude survival based on cardiac troponin T level on admission and antiplatelet therapy use.

