Cardiac troponin T as a predictor of short- and long-term mortality in community-acquired pneumonia

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Short title: Cardiac troponin T in CAP

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Keywords: biomarker, cardiac troponin T, community-acquired pneumonia, mortality

Abbreviations

ACE - acute cardiovascular event

CAP - community-acquired pneumonia

COPD - chronic obstructive pulmonary disease

CRP - C-reactive protein

cTnT - cardiac troponin T

CURB65 - confusion, urea > 7mmol/l. respiratory rate ≥ 30 breaths/minute, blood pressure (systolic < 90mmHg and/or diastolic ≤ 60mmHg), and age ≥ 65years

CVE - cardiovascular events

PCT – procalcitonin

PSI - pneumonia severity index

The association between severe community-acquired pneumonia (CAP) and a significantly heightened risk for development of an acute cardiovascular event (ACE), most commonly acute myocardial infarction, new onset arrhythmia and new or worsening cardiac failure, is well recognised, with the risk persisting for several years after recovery, and contributing significantly to both short- and long-term mortality.[1,2] Although pre-existing congestive heart failure, older age and severity of pneumonia have been identified among the risk factors for the development of these ACEs, they may also occur in relatively young individuals without underlying cardiac disease or apparent risk factors for cardiovascular events.[3] The predisposing roles that other comorbidities linked to the susceptibility to the development of CAP and its associated mortality, such as other types of chronic cardiac disease, liver, renal and

respiratory disorders, and diabetes mellitus,[4,5] may play in the development of CVEs remain to be established.

The immunopathogenesis of CAP-associated ACEs is currently the subject of considerable research interest. If pre-existing comorbidities are documented to be important predisposing factors, this may implicate chronic, low-grade systemic inflammation and associated pro-thrombotic tendencies. Infection-driven systemic inflammation superimposed on this already labile, pro-inflammatory environment is likely to trigger a hyperinflammatory, pro-thrombotic state following exposure of cells of the innate immune system, as well as platelets and structural cells, to pathogen-derived triggers such as bacterial endotoxin.[6]

Recognition of the risk to survival posed by CAP-associated ACEs has prompted considerable interest and effort in identifying reliable, systemic, host-derived biomarkers of myocardial damage (e.g. midregional proadrenomedullin, prohormone forms of atrial natriuretic peptide, cardiac troponins, and copeptin), as well as non-specific host-derived biomarkers of inflammation [e.g. cortisol, procalcitonin (PCT) and C-reactive protein (CRP)] which may act as predictors of both short- and long-term mortality in patients with CAP and ideally identify those patients at highest risk for the development of life-threatening ACEs.

A number of studies have advocated the utility of measurement of blood atrial natriuretic peptides, in particular, in predicting both short- and long-term mortality in patients with CAP[7-9] most of which have documented that their predictive value is generally equivalent to that of clinical scoring systems (PSI and/or CURB65). One

recent systematic review and meta-analysis concluded that midregional proadrenomedullin was "predictive of increased complications and higher mortality rates in patients suffering from CAP",[10] while another reported the following order of accuracy of a range of biomarkers in predicting short-term mortality in CAP: proadrenomedullin ≥ prohormonal atrial natriuretic peptides > cortisol > procalcitonin > copeptin > CRP.[11] Although these biomarkers were able to predict mortality with "good-to-moderate" accuracy, the authors reported that they had no clear advantage over CAP-specific clinical scores.[11]

In what appears to be the only study to date to have compared the utility of measurement of high-sensitivity cardiac troponinT (cTnT) with that of another biomarker of myocardial damage, *viz.* N-terminal B-type natriuretic peptide, in patients hospitalised with CAP (n=474), Chang *et al.* found the natriuretic peptide to be a strong predictor of mortality, comparable with the PSI (adjusted OR=5.3, 95% CI 1.4-19.8, p=0.013), while cTnT lacked predictive potential (OR=1.3, CI 0.5-3.2, p=0.630).[12]

In contrast to the findings of Chang *et al.*,[12] the study by Vestjens *et al.* reported in the current issue of "Respirology" found measurement of high-sensitivity cTnT to be a "strong predictor of short- (30 day) and long-term (1–4.1 years) mortality in patients hospitalised with CAP," being a better predictor of 30-day mortality than the PSI, while the two together were complementary.[13] In this study, cTnT was measured in stored, baseline serum specimens from patients (n=295) who had participated in a previously reported clinical trial focused on the therapeutic potential of adjunctive corticosteroid therapy in CAP.[14] Patients were allocated to one of 3 groups based on

baseline cTnT concentrations (lowest = <14 ng/L, n=163, average age=54.8 years; intermediate = 14–28 ng/L, n=64, average age 72.8 years; highest = >28 ng/L, n=68, average age 76.1 years).

The initial analysis documented that relative to those with the lowest cTnT values, the group with the highest, and in some cases also the group with intermediate cTnT values, were of older age, had higher frequencies of co-morbidities, and greater usage of anti-platelet therapies (a probable additional marker of comorbidity, indicative of the possible presence of pre-existing vascular disease). Although the authors performed multivariate analysis, including potential confounding variables ("based on rational judgment") in their model, categorisation of patients based exclusively on baseline cTnT may, however, have inadvertently selected those at highest risk for severe CAP and related mortality due to other factors (such as age, comorbidities, and possibly use of anti-platelet therapies as an additional marker of comorbidity). This contention appears to be supported by the highly significant differences in the PSI scores between the group with the lowest cTnT levels and the other two groups.

A number of unusual findings were documented in the study by Vestjens *et al,*[13] that are not adequately explained. Counterintuitively, the frequency of smoking was highest in the group with the lowest cTnT levels and smokers were noted in the multivariate analysis to have a lower long-term mortality. The authors attribute this to the fact that patients that needed corticosteroid therapy before recruitment to the original study were omitted, thus possibly excluding smokers with chronic obstructive pulmonary disease (COPD) and retaining only younger smokers without associated

COPD, a contention that the authors suggest was "supported by the younger age of smokers compared to non-smokers". One other surprising and unexplained finding was that CRP levels were highest in the group with the lowest levels of cTnT, being significantly higher than the levels in the group with the highest cTnT values.

These comments notwithstanding, the report by Vestjens *et al.*[13] does add to a growing literature on the utility of cardiac biomarkers in predicting outcome in severe CAP, while underscoring the need, as indicated by the authors, for additional studies to confirm the predictive ability of cTnT, and its potential association with cardiac injury. Such studies should also take into account the following issues: pathogen identification, antibiotic therapy, particularly co-administration of macrolides, as well as usage of statins and platelet-targeted therapies; inclusion of age-matched, non-CAP, control subjects to monitor the influence of older age and pre-existing co-morbidities on basal cTnT levels; accurate identification of the causes of death, as well as the relationship between elevated levels of cTnT and the occurrence of ACEs; and, finally, confirmation of the apparent superiority of cTnT relative to the PSI, observed in the current study,[12] as well as measurement of its predictive accuracy compared to other clinical severity scoring systems.

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