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Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: Systematic review and meta-analysis

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ABSTRACT

Background: Cardiovascular disease, especially ischemic heart disease, is a major comorbidity in chronic obstructive pulmonary disease (COPD) patients. Several studies suggested that after acute exacerbation of COPD (AECOPD), there is a significant increase of mortality (cardiac and all-cause) and of myocardial infarction. Whether cardiac troponin (Tn) elevation during AECOPD could be considered a prognostic marker of all-cause mortality is still debated.

Methods: To assess the prognostic role of cardiac Tn elevation during AECOPD, we performed a systematic review and meta-analysis. We included studies with patients admitted to the hospital for AECOPD, with at least one Tn assessment and reporting the relationship (after multivariable analysis) between Tn elevation and all-cause mortality. Secondarily, studies were stratified according to: i) type of troponin (Tn I or Tn T), and ii) follow-up length (≤6 months vs. >6 months).

Results: Ten studies were included in the systematic review and 8 in the meta-analysis. Cardiac Tn elevation ranges from 18% to 73%. We found that cardiac Tn elevation was significantly related to an increased risk for all-cause mortality (OR 1.69; 95% CI 1.25–2.29; I^2 40%). This finding was independent to the follow-up length of studies (≤6 months: OR 3.22; 95% CI 1.31–7.91; >6 months: OR 1.38; 95% CI 1.02–1.86). Finally, Tn T seems to be more helpful in predicting all-cause mortality as compared to Tn I (OR 1.54; 95% CI 1.2–1.96 vs. OR 3.39, 95% CI 0.86–13.36, respectively).

Conclusions: In patients admitted to the hospital for AECOPD, cardiac Tn elevation emerged as an independent predictor of increased risk of all-cause mortality.

1. Introduction

Comorbidities are common at any severity degree of chronic obstructive pulmonary disease (COPD) [1,2]. Cardiovascular disease (CVD) is a major comorbidity in COPD patients [1,2]. Particularly, ischemic heart disease (IHD) and COPD are among the principal causes of mortality and morbidity in western countries and are frequently associated [1,2]. IHD as well as heart failure or pulmonary embolism (PE) are reported as the main causes of death for patients affected by COPD [2,3]. The natural history of at least one third of COPD patients is characterized by recurrent episodes of acute exacerbation (AECOPD) [2]. These episodes of AECOPD increase the risk of mortality (cardiac and all-cause) and of myocardial infarction (MI) [2–5]. Several authors attempted to understand whether elevation of cardiac troponin (Tn) during AECOPD, in the absence of signs and symptoms suggestive of concomitant MI, could discriminate patients at higher mortality risk [6–15]. The results are conflicting and the prognostic role of Tn elevation in AECOPD is still uncertain. Differences in inclusion/exclusion criteria, sample size, type of Tn, follow-up and endpoint's definition between

Abbreviations: IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of COPD; Tn, troponin; HR, hazard ratio; OR, odds ratio; URL, upper reference limit; PRISMA, preferred reporting items for systematic reviews and meta-analyses; QUOROM, quality of reporting of meta-analyses; MOOSE, meta-analysis of observational studies in epidemiology; HS, high sensitivity; HF, heart failure; MI, myocardial infarction.

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various studies may contribute to explain these discrepancies [6–15]. Consequently, Tn measurements are not systematically used to manage AECOPD patients in daily clinical practice. Systematic reviews employing meta-analytic techniques provide quantitative and objective means to pool and assess available clinical evidence, emphasizing internal validity and homogeneity. Therefore, we performed a comprehensive systematic review and meta-analysis of available studies to assess the value of cardiac Tn elevation to predict all-cause mortality in patients admitted to the hospital for AECOPD.

2. Methods

We performed a systematic review and meta-analysis following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement and the recommendations from The Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [16–19].

2.1. Search strategy

Appropriate articles were found using the MESH strategy and searching in MEDLINE, Cochrane Library, Google Scholar and BioMed Central database. We selected only articles published in English. The terms searched were: ((“pulmonary disease, chronic obstructive”[MeSH Terms] OR (“pulmonary”[All Fields] AND “disease”[All Fields] AND “chronic”[All Fields] AND “obstructive”[All Fields]) OR “chronic obstructive pulmonary disease”[All Fields] OR “copd”[All Fields]) AND (“troponin”[MeSH Terms] OR “troponin”[All Fields])). The research was carried out between December 2014 and February 2015. Independent reviewers (AF, SB, GC) analyzed the articles, first by valuing the title and abstract to decide which one needed a full paper evaluation. All reviewers reached a consensus on the final number of studies to include in the analysis. The criteria for inclusion were: i) observational studies of patients admitted to the hospital for AECOPD; ii) more than 50 patients included in the analysis; iii) at least one determination of cardiac Tn during the hospitalization; iv) classification of patients according to elevation or not of cardiac Tn values; v) relationship between cardiac Tn elevation and all-cause mortality, expressed as hazard ratio (HR) or odds ratio (OR) at multivariate analysis; and vi) studies published from year 2000. We did not include: i) interventional studies, ii) those not published in English, iii) those referring to animals, and iv) duplicate.

2.2. Data extraction, definition and end-points

Independent reviewers (AF, SB, GC) completed the database, which contained data about the journal, year of publication, authors, baseline characteristics of the population included, and type of Tn (I or T, high sensitivity (HS) or no HS). Finally, all factors considered at uni- and multivariate analyses were collected. In all studies patients were stratified into two groups according to the elevation or not of cardiac Tn. Cardiac Tn elevation was defined as at least one value above the cut-off for positivity of the test (upper reference limit, URL). Only in one study, was cardiac Tn elevation defined according ROC analysis and not URL [8]. The primary endpoint was the incidence of all-cause mortality. As complementary analyses, we considered the relationship between Tn elevation and all-cause mortality, stratifying for: i) patients with AECOPD and value of Tn T vs. patients with AECOPD and value of Tn I; and ii) studies with a follow-up $\leq$6 months vs. those with follow-up >6 months.

2.3. Internal validity and quality appraisal

The quality of included studies was independently evaluated by two other unblinded reviewers (RP, FDA), on pre-specified electronic forms, which were piloted over the first 5 cases, with divergences resolved after consensus. Modifying the MOOSE item list in order to take into account the specific features of included studies, we separately abstracted and appraised study design, setting, data source, and statistical methods for multivariable analysis, as well as, in keeping with The Cochrane Collaboration approach, the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias).

2.4. Data analysis and synthesis

Continuous variables are reported as mean ($\pm$ standard deviation) or median ($\pm$ interquartile). Categorical variables are expressed as number and percentage (%). Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method [20], computing risk estimates with 95% confidence intervals according to logarithmic transformation of the hazard measures, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Considering the high likelihood of between-study variance, we used a random effect model. Statistical heterogeneity was assessed using the Cochran's Q test. This statistic is complemented with the I^2 statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0 to 25% represents insignificant heterogeneity, 26 to 50% low heterogeneity, 51 to 75% moderate heterogeneity, and >75% high heterogeneity [21].

3. Results

3.1. Search results and study selection

After removal of duplicates, 302 studies were analyzed with database search. 276 studies were excluded after the first evaluation of the title and abstract, as they did not meet pre-specified inclusion and exclusion criteria. Twenty-five reports were screened and analyzed. Fifteen studies were excluded from analysis: two were just abstracts, one was a comment on previous data, three included only patients with a stable phase of COPD, one failed to provide complete data on troponin, one was a secondary analysis of previously published data [22] and seven did not provide complete information on outcome. It follows that 10 articles were included in the systematic review and 8 in the meta-analysis (Fig. 1). Particularly, the studies of Youssef et al. and Martins et al. [9,14] were excluded from the meta-analysis because the outcome was not expressed as HR or OR (Fig. 1). Tables 1 and 2 summarize the main characteristics of these studies.

3.2. Patient characteristics

A total of 2295 patients were included. Mean age of the population was 74 years and 42% were female. In one study, we were not able to discriminate if patients with concomitant MI were considered in the outcome analysis (Table 1). In the other 9 studies, MI diagnosis was considered exclusion criteria or did not influence the results (Table 1). Overall, cardiac Tn elevation was present in the 51% (95% CI 48%–53%) of patients admitted to the hospital for AECOPD and ranged between 18% and 73%. Cardiovascular risk factors of the population are reported in Table 3. Of note, all studies reported only one value of HR or OR for all-cause mortality associated with the elevation of cardiac Tn, with the exception of the study by Marcun et al. [12]. In this study, the authors reported the HR values for both Tn at the admission and at discharge [12].