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Amino terminal pro brain natriuretic peptide predicts all-cause mortality in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis

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Abstract

Natriuretic peptides (NPs) are a family of prognostic biomarkers in patients with heart failure (HF). HF is one of the most frequent comorbidities in patients with chronic obstructive pulmonary disease (COPD). However, the prognostic role of NP in COPD patients remains unclear. The aim of this meta-analysis was to evaluate the relation between NP and all-cause mortality in COPD patients. We performed a systematic review and meta-analysis of observational studies assessing prognostic implications of elevated NP levels on all-cause mortality in COPD patients. Nine studies were considered for qualitative analysis for a total of 2788 patients. Only two studies focused on Mid Regional-pro Atrial Natriuretic Peptide (MR-proANP) and brain natriuretic peptide (BNP), respectively, but seven studies focused on pro-BNP (NT-proBNP) and were included in the quantitative analysis. Elevated NT-proBNP values were related to increased risk of all-cause mortality in COPD patients both with and without exacerbation (hazard ratio (HR): 2.87, $p < 0.0001$ and HR: 3.34, $p = 0.04$, respectively). The results were confirmed also after meta-regression analysis for confounding factors (previous cardiovascular history, hypertension, HF, forced expiratory volume at 1 second and mean age). NT-proBNP may be considered a reliable predictive biomarker of poor prognosis in patients with COPD.

Keywords

Chronic obstructive pulmonary disease, NT-proBNP, mortality, outcome, exacerbation

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Introduction

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are both associated with adverse long-term outcome.[1] Cardiovascular disease (CVD) represents the most common comorbidity in patients with COPD and is related to increased mortality.[2] Particularly, HF is the most frequently associated disease, affecting up to a 30% of COPD patients.[3,4] Natriuretic peptides (NPs) are a family of biomarkers released from the heart in response to myocardial wall stress. The most known NP is the brain natriuretic peptide (BNP) and it's derived amino-terminal pro-BNP (NT-proBNP). These are validated markers of impaired myocardial function and they are routinely used in the stratification of acute and chronic HF patients.[5,6] Current guidelines suggest the use of both BNP and NT-proBNP in daily clinical practice for diagnosis and management of HF patients.[6] They are also a well-validated prognostic biomarker for CVDs.[6] Similarly, COPD patients exhibit higher levels of NT-proBNP, especially during acute exacerbations of the disease, and a prognostic role for all-cause mortality in this population has been suggested.[7–15]

To confirm this hypothesis, we have conducted a systematic review and a meta-analysis of the studies assessing the relation between elevated levels of NP on all-cause mortality in COPD patients.

Methods

We performed a systematic review and meta-analysis following the preferred reporting items for systematic reviews and meta-analyses amendment to the quality of reporting of meta-analyses statement and the recommendations from The Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology.[16–19]

Search strategy

Appropriate articles were found using MESH strategy and searching in MEDLINE, Cochrane Library, Google Scholar and BioMed Central database. The research was carried out in February 2016. The terms searched were as follows: ((brain natriuretic peptide) OR (BNP) OR (NT-proBNP) OR (MR-proANP) OR (atrial natriuretic peptide)) AND ((COPD) OR (chronic obstructive pulmonary disease) OR (acute exacerbation of chronic obstructive pulmonary disease) OR (AECOPD)) AND ((mortality) OR (heart failure)). Independent reviewers (AP and SB) analysed the articles, first analysing the title and abstract and then valuating which study 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 as follows: (i) observational studies of patients with COPD; (ii) more than 50 patients; (iii) determination in at least one blood sample of NP value; and (iv) relationship between NP value and all-cause mortality, expressed as hazard ratio (HR) or odds ratio (OR) at multivariate analysis. We did not include (i) interventional studies, (ii) those involving animals and (iii) duplicates.

Data extraction, definition and endpoints

Independent reviewers (FZ, GT and GS) completed the database, which contains data about the journal, year of publication, authors, baseline characteristics of the population included, NP measured and cut-off used for the analysis. All factors considered at uni- and multivariate analysis were collected. The primary endpoint was the incidence of all-cause mortality in patients with and without acute exacerbation of COPD (AECOPD) stratified according NP values. Secondary analyses were done stratifying the study population in (i) patients with versus without AECOPD; (ii) studies with a follow-up length $\leq$1 year versus those with follow-up >1 year; and (iii) studies enrolling patients with previous HF diagnosis versus studies enrolling patients without previous HF.

Internal validity and quality appraisal

The quality of included studies was independently evaluated by two other unblinded reviewers (RP and FG), on pre-specified electronic forms, which were piloted over the first three cases, with divergences resolved after consensus. For the assessment of quality, the modified version of the New Castle Ottawa quality assessment scale was used[20] even if neither a study was excluded on the basis of this approach. The same authors independently verified the eventual exclusion of some study analysing references of all the papers valued. 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) was analysed using the Cochrane Collaboration approach.

Data analysis and synthesis

Continuous variables were reported as mean (±standard deviation) or median [interquartile range]. Categorical variables were expressed as number and percentage (%). Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method,[21] computing risk estimates with 95% confidence intervals (CIs) according to logarithmic transformation of the hazard measures. Considering the high likelihood of between-study variance, a random effects model was used. 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 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and >75% high heterogeneity.[22] Random effects meta-regression analysis was performed to assess the effect of some potential confounding factors (previous diagnosis of CVD , HF, hypertension, mean value of forced expiratory volume at 1 second (FEV_1) and mean age of the population) on results. χ^2 Test was used to test the difference between subgroups. Publication bias was appraised by graphical valuation of funnel plots and through Begg and Mazumdar rank correlation, Egger's regression intercept and Duval and Tweedie trim and fill. The software used to carry out the analysis were ProMeta Software (Version 2; Internovi, Italy) and RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Search results and study selection

After removal of duplicates, 438 studies were analysed with database search (Figure 1). Forty-four reports were screened as full paper and analysed (Figure 1). Thirty papers were excluded from analysis, because 4 were reviews, 1 was a clinical case, 3 studies were conducted on less than 50 patients and 22 did not show data on mortality (Figure 1). It follows that 14 articles were assessed for eligibility, but 2 were discarded because they were the duplicates of a previous study population, one because displayed data on a population with non-specific chronic pulmonary disease and second one because did not have complete data on outcome (Figure 1). Finally, nine studies were included in the qualitative analysis and seven studies in the quantitative analysis. We excluded from the meta-analysis the study of Bernasconi et al. because it was the only one using the dosage of MR-proANP[14] and the study of Stoltz et al. because the data about the outcome were not expressed as HR or OR and the NP dosed was BNP.[15] Tables 1 and 2 summarize the main characteristics of the studies.

Study population

A total of 2788 patients were included. Mean age of the population was 61.1 ± 16.5 years and 57% were male. The total number of deaths was 453 (16%). Criteria for COPD diagnosis are reported in Table 1. In the study of Medina et al., the 69% of patients had smoke-related COPD (Table 2).[8] Overall, seven studies were focused on patients admitted to hospital for AECOPD[8,10–15] (Table 1). The 53% of the patients were current smokers. Mean FEV_1 in patients with AECOPD was 0.89 ± 0.6 L, whereas it was 2.6 ± 0.1 L in patients with stable COPD. A previous diagnosis of hypertension was present in 21% of patients, while a previous diagnosis of HF or CVD was detected in 2% and 20% of the population, respectively (Table 2). However, CVD and HF definitions were not homogeneous across different studies (Table 2).[7,10–15]

Quantitative analysis

In the seven studies considered in the meta-analysis, the NP measured was NT-proBNP[7–13](Table 2) and this was dosed by the same assay (Elecsys® NT-proBNP, Roche Diagnostics, Rotkreuz, Switzerland). Patients were stratified according to NT-proBNP value (above vs. below the cut-off), although the cut-off differed among the studies. In fact, van Gestel et al. stratified the population using an NT-proBNP value ≥500 pg/mL,[7] whereas Chang et al. according to the commonly value considered in hospital laboratory (220 pmol/L).[10] Medina et al. defined the NT-proBNP cut-off after Receiver Operator Characteristic (ROC) curve analysis for the population.[8] Stamm et al. and Campo et al. divided the study population according to the median values of NT-proBNP.[9–13] Finally, Hoiseth et al. used the value of the NT-proBNP above the tertile limit[11] as cut-off (Table 2).

Quantitative analysis

NT-proBNP values above the considered cut-off were associated with an increased risk of all-cause

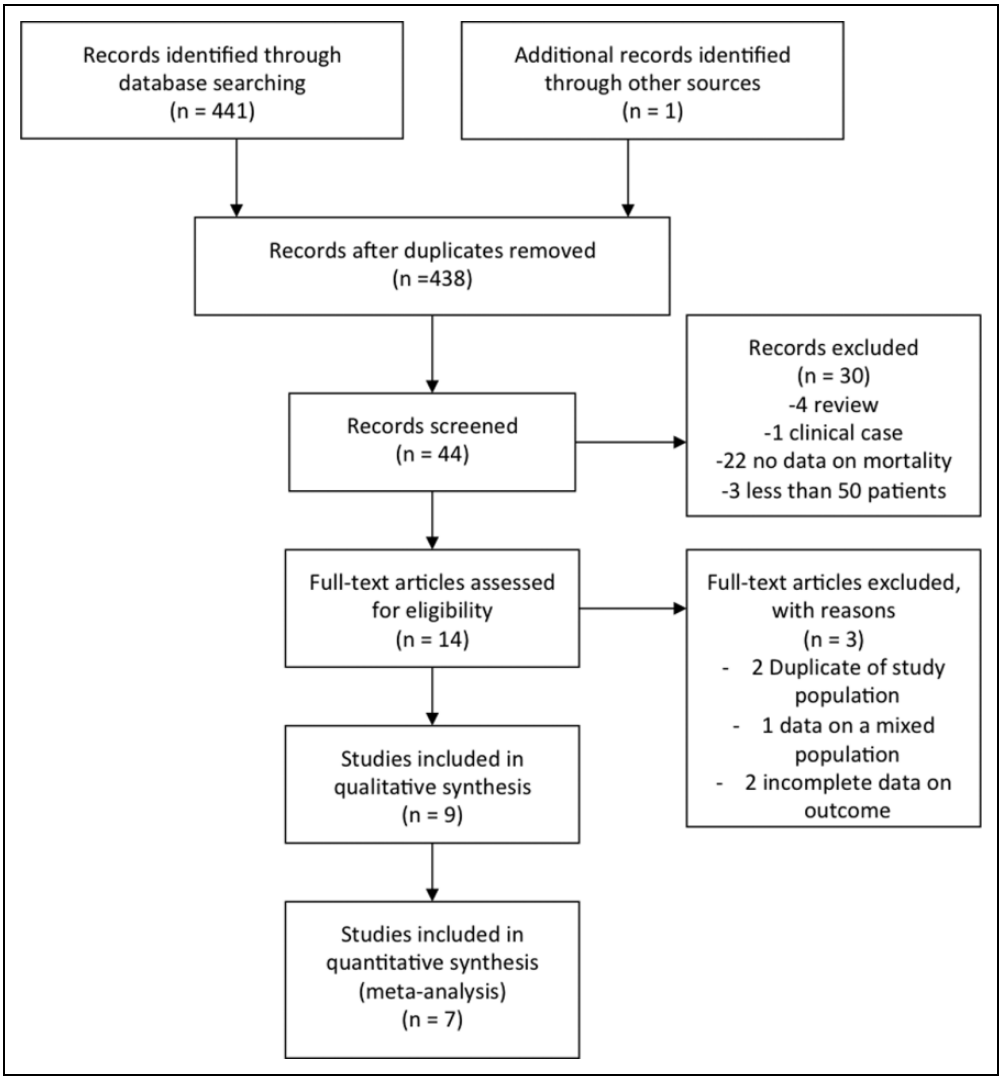

Figure 1. Outline of search strategy. N: number.

mortality both in AECOPD patients (HR: 2.87, 95% CI: 1.70–4.84, I^2: 45%) and in patients without AECOPD (HR: 3.34, 95% CI: 1.04–10.77, I^2: 52%; Figure 2). The results of the χ^2 test showed the absence of statistical significant difference between the two subgroups ($\chi^2 = 0.06$; $p = 0.81$), with an over-all effect size of 2.80 ($p < 0.00001$). Of note, in the subgroup of patients hospitalized for AECOPD, all the cut-off used were above the 300 pg/mL (Table 2), the usual cut-off for exclusion of HF in patients with acute dyspnea or worsening of symptoms as suggested by current guidelines.[6]

We also carried out the analysis for follow-up length. The predictive value of NT-proBNP was present independently by the length of the follow-up both in AECOPD and in non-AECOPD patients (Table 3, Online Supplemental Figures 2s and 3s). Of note, the HR for studies with follow-up length of 1 year or less was 4.45 ($p < 0.0001$) and was twice the HR of studies with longer follow-up (HR: 2.01, $p = 0.002$). However, the significance for the test for subgroup differences was 0.06.

Meta-regression analysis displayed the absence of interaction between the elevated level of NT-proBNP and all-cause mortality and previous diagnosis of CVD ($\beta = -0.01$; $p = 0.522$), hypertension ($\beta = -0.02$; $p = 0.614$), FEV_1 values ($\beta = 0.34$; $p = 0.438$), mean age of the population ($\beta = -0.03$; $p = 0.614$) and HF ($\beta = 0.03$; $p = 0.233$). In particular, the subgroup analysis for studies enrolling patients without previous HF diagnosis versus those enrolling patients with HF diagnosis also showed the absence of statistical significance (HR: 3.1, 95%CI: 1.89–4.77 vs. HR: 4.06, 95% CI: 2.06–7.09,

Table 1. Main characteristics of the studies.

Study	Ref	Prospective	Main diagnosis of patients	COPD diagnosis based on	AECOPD	Follow-up length	Number of deaths	Confounding factors at uni- and multi-variable analyses
van Gestel et al.	7	Y	Surgery of AAA	Spirometry GOLD criteria	N	1 year and 3 years	23	Sex, age, diastolic function, surgery site, renal dysfunction, hypertension, smoke, cardiac risk index
Medina et al.	8	Y	Acute chronic pulmonary disease	NA	Y	1 year	22[a]	Sex, age, cardiac rhythm, creatinine concentration
Stamm et al.	9	N	Tobacco exposed patients from COPD registries	Spirometry GOLD criteria	N	564 (252–826) days	NA	Sex, age, severity of lung disease
Chang et al.	10	Y	Hospital admission for AECOPD	Clinical history	Y	30 days	21	Age, lung function, arterial blood gases, BMI, CURB65
Hoiseth et al.	11	Y	Hospital admission for AECOPD	Spirometry BTS criteria	Y	1.9 years	57	Sex, age, creatinine, BMI, HF, AF, peripheral oedema, cephalization of lung veins, CRP, troponin
Marcun et al.	12	Y	Hospital admission for AECOPD	GOLD criteria (stage II–IV)	Y	6 months	17	Age, sex, GOLD stage, left ventricular dysfunction, NT-proBNP (at admission/ discharge, reduction of >30%), troponin (admission and discharge), troponin and NT-pro-BNP (admission and discharge)
Campo et al.	13	N	Hospital admission for AECOPD	Spirometry clinical history	Y	701 (374–1016) days	231	Age, sex, DM, hypertension, dyslipidemia, smoking, IHD history, WBC, Hb, PLT, fibrinogen, CRP, CV drugs, arterial blood gases, creatinine, troponin elevation
Bernasconi et al.	14	Y	Hospital admission for AECOPD	Clinical history, GOLD criteria	Y	2 years	37	Charlson condition and age-related score, BMI, leukocyte counts, CRP, FEV_1% predicted, PaO2, PaCO2, pulmonary hypertension
Stolz et al.	15	Y	Hospital admission for AECOPD	Clinical history, spirometry, GOLD criteria	Y	2 years	46	NA

Ref: reference; COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD; Y: yes; N: no; AAA: abdominal aortic aneurism; BTS: British Toracic Society; NA: not available; GOLD: Global Initiative for Chronic Obstructive Lung Disease; WBC: white blood count; CRP: C-reactive protein; BNP: type B natriuretic peptide; BMI: body mass index; AF: atrial fibrillation; Hb: haemoglobin; PLT: platelets; IHD: ischemic heart disease; DM: diabetes; CV: cardiovascular; FEV_1: forced expiratory volume in 1 second.
[a]Data on total study population.

Table 2. Main characteristics of the study population.

Study	Ref	Patients (*n*)	Age [IQR] (SD)	Male sex (%)	FEV_1 (L)	Previous CVD (%)	Criteria for CVD	Previous HF (%)	Smoke (%)	Hypertension (%)	Natriuretic peptide assessed	NP median [IQR] (pg/mL)	NT-proBNP cut-off (pg/mL)
van Gestel et al.	7	261	68 (10)	206 (78)	2.6 ± 0.8	11 7 8	MI CR Angina	4	31	51	NT-proBNP	NA	500
Medina et al.	8	133	75 [41–95][a]	151 (79)[a]	NA	Exclusion criterion	–	Exclusion criterion	100	NA	NT-proBNP	517 [198–1212]	587.9[b]
Stamm et al.	9	498	64 (8)[a]	430 (54)[a]	NA	Exclusion criterion	–	Exclusion criterion	100	NA	NT-proBNP	49 [22–94]	49
Chang et al.	10	250	72 (11)	112 (46)	0.81 ± 0.34	31	CVD	NA	97	NA	NT-proBNP	18.1 [0.54–1062][c]	1695
Hoiseth et al.	11	99	72 (9)	53 (53)	0.91 ± 0.45	27	CAD	14	48	31	NT-proBNP	423 [264–909]	909
Marcun et al.	12	127	70 (10)	89 (70)	0.9 ± 0.46	7	IHD	31	100	43	NT-proBNP	NA	NA
Campo et al.	13	694	76 (10)	369 (53)	NA	34	IHD	Exclusion criterion	23	54	NT-proBNP	884 [291–2817]	884
Bernasconi et al.	14	167	70 (42–91)	75 (45)	0.89 ± 0.4	76	Cardiopathy	7	NA	25	MR-proANP	95.9 [52.5–166.3]	NA
Stolz et al.	15	208	70 (9.9)	94 (45)	0.93 ± 0.41	91	Cardiopathy	NA	92	13	BNP	65 [34–189]	NA

Ref: reference; NA: not available; MI: myocardial infarction; CVD: cardiovascular disease; CAD: coronary artery disease; CR: cardiac revascularization; IHD: ischemic heart disease; IQR: interquartile range.

[a]Data on total population.

[b]Cut-off from ROC curve analysis.

[c]In the original paper, the NT-proBNP values were expressed as pmol/L, as conversion factor we applied the formula: 1 pg/mL = 0.118 pmol/L.[21]

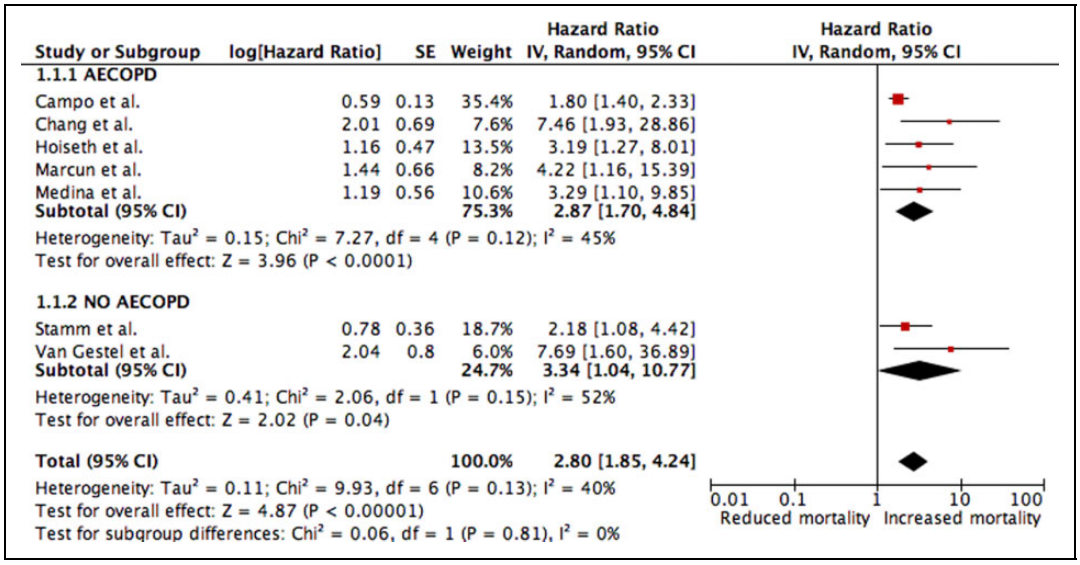

Figure 2. Relationship between NT-proBNP above the cut-off and all-cause mortality. Data are displayed for each available study. Error bars represent 95% CIs. SE: standard error. CI: confidence interval.

Table 3. HR for the relationship between NT-proBNP above the cut-off and all cause-mortality stratified by follow-up length in patients with COPD with and without exacerbation.

	≤ 1 year follow-up length				>1 year follow-up length			
	HR (95% CI)	I^2 (%)	χ^2	*P*	HR (95% CI)	I^2 (%)	χ^2	*p*
AECOPD	4.45 (2.18–9.06)	0	3.51	0.06	2.01 (1.30–3.10)	27	1.19	0.28
NO AECOPD	7.69 (1.60–36.89)	[a]			2.86 (1.24–6.59)	28		

COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD; HR: hazard ratio; CI: confidence interval.
[a]Data on only van Gestel study.[7]

respectively, χ^2 test: 0.51, $p = 0.47$) (Online Supplemental Figure 1s). Finally, the funnel-plot analysis showed the presence of possible publication bias with four trimmed studies (Figure 3). Both Begg and Mazumdar rank correlation (Z value for Kendall $\tau = 1.95$, $p = 0.011$) and Egger's regression intercept (intercept = 1.79; $t = 7.34$; $p = 0.001$) confirmed this finding. Of note, the estimated effect of NT-proBNP after trim and fill analysis remained predictive for all-cause mortality (OR: 3.04, 95% CI: 2.18–4.25).

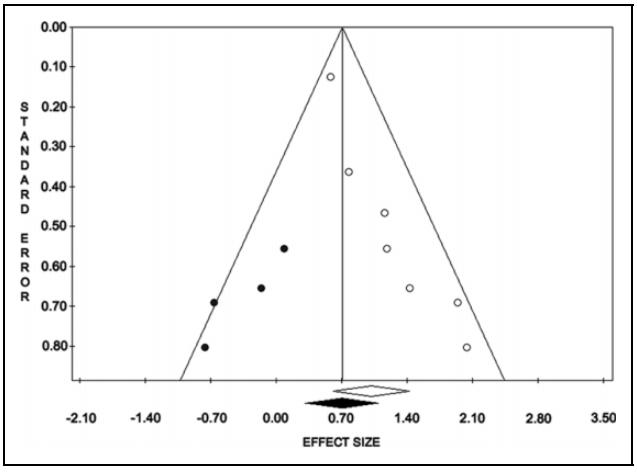

Figure 3. Funnel plot of study included in the meta-analyses.

Discussion

Our meta-analysis has clearly illustrated that elevated levels of NT-proBNP are related to all-cause mortality in patients with COPD with or without exacerbation of the disease. The predictive value of elevated level of NT-proBNP is not related to prior CV history. With meta-regression analysis, we found that a previous history of CVD and hypertension, common causes of NP elevation, did not influence the relationship between NT-proBNP and all-cause mortality in COPD patients and this was confirmed also for

previous diagnosis of HF, which was verified also after subgroup analysis. Finally, the predictive value of elevated NT-proBNP levels is maintained both at long- and short-term follow-up.

Similar results were obtained and confirmed by Bernasconi et al.[14] This study showed a predictive value on all-cause mortality at 2 years also for the MR-proANP, another NP molecule. Instead, in the study of Stoltz et al., the dosage of the BNP failed to predict both short- and long-term mortality rates. Being the only two studies dosing NP different from NT-proBNP, we decided to include these studies only in the qualitative, but not in the quantitative, analysis.

NT-pro BNP is a well-established index of cardiac chamber overload. Although the studies included in the meta-analysis do not provide any mechanistic reason to explain the NT-proBNP elevation in COPD patients, some speculations may be reasonable. Right ventricular overload may occur in COPD patients because of pulmonary hypertension,[23] resulting from vasoconstriction secondary to hypoxia,[24] increased shear stress secondary to the chronic inflammation status[25] and pulmonary embolism.[26] COPD is also associated with an increased burden of left-sided CVDs.[27,28] The most common diseases are undiagnosed coronary artery disease,[25] stress cardiomyopathy,[29] HF and cardiac arrhythmias (i.e. atrial fibrillation).[30,31] However, the strength of our data is related to the fact that the prevalence of CVD in the study population was very low. CVD ranges between 7% and 34%, whereas HF ranges between 4% and 31%. This finding suggests that the presence of an increase in NP levels should be related to different causes rather than prior CV history or HF. Nevertheless, due to the high heterogeneity between the definitions of CVD across studies (varying between previous cardiac revascularization, angina, previous myocardial infarction and cardiopathy), new analyses are necessary to better define this finding. At the same time, as recently demonstrated by Hilde et al., a mild impairment of right ventricle function is present also in COPD patients with only a slight increase in mean pulmonary artery pressure.[23] So, it is possible that the release of NT-proBNP starts early in COPD patients, even when a cardiac disease has not been yet diagnosed and for this reason being predictive of the worst outcome. Obviously, more studies are needed to better define the pathophysiological mechanism behind the increase of this biomarker.

Finally, it is already known that NP levels are higher during AECOPD, but it is interesting to note that the predictive value for NT-proBNP is present also in COPD patients without exacerbation, underlying the role of the heart–lung interaction in chronic disease as well. Moreover, our meta-analysis does not state the presence of any interference between the FEV_1 values and the predictive value of NT-proBNP, hinting the possible absence of a relation between the predictive value of the biomarker and the severity of the pulmonary disease.

To the best of our knowledge, this is the first meta-analysis showing that elevated level of NT-proBNP in COPD patients is predictive for all-cause mortality. Our findings suggest the role of NT-proBNP as a relevant prognostic biomarker not only for patients with cardiac pathological conditions but also with chronic pulmonary disease.

Our findings carry an important clinical implication. The presence of this inexpensive biomarker in COPD patients could be helpful to perform stratification for prognosis. It may be able to select a subgroup of COPD patients at higher risk, requiring more attention and treatment optimization. The predictive value of elevated BNP levels on mortality has been already tested in several clinical scenarios, different from acute coronary syndrome or HF, such as sepsis, renal failure, cancer and stroke.[32–36] This is the first meta-analysis investigating the predictive role of BNP on mortality in COPD patients. Our results could be considered hypothesis generating and they can suggest the introduction in clinical practice of the dosage of BNP level in every COPD patients, in association with other cardiac biomarker (such as troponin), with the aim to define new algorithms to predict the risk of death or CV versus respiratory death in COPD patients (both with and without exacerbation) and to better assess the presence and the degree of heart and lung disease. Finally, it is also necessary to define the most sensitive and predictive cut-off of this marker in COPD population and to understand the pathophysiological mechanisms responsible of its increase.

Study limitations

This is a study-level meta-analysis of observational studies and for this reason our meta-analyses have several intrinsic limits. First, we did not have enough data to weigh how much the presence of some confounding factors impact on results. It is well known that the dosage of NP and cut-off changes in reason of the renal function and of the age of the patients. However, data available were not adequate enough to

analyse the impact of those population characteristics. Second, even if we had data about FEV_1, we were not able to perform meta-regression analysis on the degree of severity of the COPD in each study population (e.g. stratifying the population in Global Initiative for Chronic Obstructive Lung Disease classes) or on other important respiratory parameters that could influence the pathophysiological mechanism of the increase of NP (e.g. PaO_2, $PaCO_2$, mean respiratory rate) and so the relation with all-cause mortality. Moreover, the analysis is limited to all-cause mortality and we were not able to discriminate between cardiac, pulmonary or other causes of death. Factors evaluated in the logistic regression were not homogenous between the studies, because they were tailored to different goals. Finally, analysis showed the presence of publication bias. This could be related to the fact that every single study of NT-proBNP was related to a negative outcome and there are no studies reporting the absence of relationships with all-cause mortality and this biomarker. At the same time, Stolz et al. reported the absence of predictive value for BNP, but unluckily we were not able to use this study because it was the only one using the dosage of BNP.

Conclusion

Increased NT-proBNP levels are significantly related to all-cause mortality in COPD patients with and without acute exacerbation of the disease, regardless the presence of previous CV history.

Declaration of conflicting interests

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Supplemental material

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