Early View

Original article

Cardiac biomarkers and long-term outcomes of exacerbations of COPD: a long-term follow-up of two cohorts

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Abstract:

Background: Chronic obstructive pulmonary disease (COPD) patients often have cardiac comorbidities. Cardiac involvement at the time of a COPD exacerbation is associated with a high short-term mortality, but whether this influences long-term outcomes is unknown. We explored whether biomarkers of cardiac dysfunction at the time of a COPD exacerbation predict long term outcomes.

Methods: Two prospective cohorts of patients admitted to Waikato hospital for exacerbations of COPD were recruited during 2006-2007 and 2012-2013. N-terminal proBNP (NT-proBNP) and troponin T were measured on admission and were used to indicate cardiac stretch and myocardial injury respectively. Five-year survival after discharge and subsequent admissions for cardiac disease and COPD exacerbations were analysed using Kaplan-Meier and Cox proportional hazards tests.

Results: The overall 5-year mortality was 61% . Patients with high NT-proBNP on admission had higher mortality than those with normal cardiac biomarkers (adjusted Hazard Ratio (aHR) 1.76, 95% CI 1.18-2.62). High NT-proBNP was also associated with a higher risk of future cardiac admissions (aHR 1.75 95% CI 1.2-2.55). Troponin T levels were not associated with long-term survival (aHR 0.86 95 CI 0.40-1.83) or future cardiac admissions (aHR 0.74, 95% CI 0.34-1.57). Neither biomarker predicted future COPD exacerbations.

Conclusion: The long-term prognosis following a hospitalisation for an exacerbation of COPD is poor with less than half of patients surviving for 5 years. Elevated NT-proBNP at the time of a COPD exacerbation is associated with higher long-term mortality and a greater likelihood of future cardiac admissions, but not future COPD exacerbations.

Introduction:

Cardiovascular disease is an important co-morbidity in chronic obstructive pulmonary disease (COPD) patients and is estimated to cause up to 37% of deaths[1, 2]. People with COPD have a high risk of cardiovascular disease because of the shared risk factors of advancing age and smoking, which contribute to the pathophysiology of both conditions[3]. However, lung and cardiovascular disease frequently coexist even in non-smokers, indicating that there are other mechanisms linking these diseases.

Cardiac co-morbidities are particularly important in the setting of acute exacerbations of COPD. Several studies have documented high rates of myocardial infarction, arrhythmias, and heart failure among patients experiencing exacerbations of COPD and these are associated with a worse short-term prognosis[4-9]. Exacerbations of COPD, heart failure, and acute coronary syndromes can all present as dyspnoea or chest discomfort and it is likely that cardiovascular disease is under-diagnosed in patients with COPD exacerbations leading to under-treatment[4].

We have previously reported on two prospective observational cohort studies of biochemical evidence of cardiac pathology in patients admitted to hospital for acute exacerbations of COPD without clinical evidence of acute cardiac disease[10-13]. The first study (cohort 1) found that 28% of participants had elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and 17% had elevated troponin T[10]. Elevated cardiac biomarkers were associated with substantially higher 30-day mortality. These findings were confirmed in the second study (cohort 2)[12]. These biomarkers appear to indicate acute or chronic cardiac involvement that cannot be reliably detected by clinical assessment, routine chest radiographs, or electrocardiograms[13]. Furthermore, the elevated cardiac biomarkers are associated with both left and right heart dysfunction[14].

Thus cardiac involvement has at least short-term prognostic significance in the setting of COPD exacerbations.

The long-term prognosis after hospitalisation for an exacerbation of COPD is poor, with a 5-year mortality survival of around 60%[4]. It is unknown to what extent sub-clinical cardiac involvement influences this prognosis beyond the acute phase of the COPD exacerbation.

To test the hypothesis that elevated biomarkers of cardiac injury (troponin) and cardiac stretch (NT-proBNP) during exacerbations of COPD would predict long-term prognosis for survival, further COPD exacerbations, and future cardiac events, we combined and analysed the data from these two prospective cohorts.

Methods:

Study participants
Two cohorts of consecutive patients admitted to Waikato Hospital for exacerbations of COPD were recruited (cohort 1, n=247 [2006-2007] and cohort 2, n=176 [2012-2013]). The details of these cohorts have been published previously[10, 11]. Each cohort recruited patients over one complete year. Patients who did not live locally or could not attend follow-up were excluded. Both cohorts recruited all consenting patients with clinically-diagnosed exacerbations of COPD, but excluding those with suspected acute cardiac disease and those with pneumonia (consolidation on chest radiographs). The second cohort also excluded patients with end-stage renal disease. For those with multiple admissions over the year, the first admission was regarded as the index admission.

All participants gave written consent at the time of study inclusion and approval was obtained for both cohorts from the New Zealand Health and Disability Ethics Committee.

Data collection
For this analysis the electronic records of patients were accessed to ascertain mortality within 5 years of discharge from hospital. We also recorded re-admissions for exacerbations of COPD and cardiac admissions with heart failure or acute coronary syndromes within the Waikato District Health Board region. Fourteen participants were recruited in both cohort 1 and 2 and were removed from cohort 2 to avoid duplication.

Cardiac biomarkers
Both cohorts collected blood for measurement of NT-proBNP and cardiac troponin T within 24 hours of admission to hospital. Measurements of NT-proBNP and troponin T were performed by Waikato Hospital laboratory using quantitative electrochemiluinescence assay. NT-proBNP levels in both cohorts had a detection limit of 0.6pmol/L (Electsys proBNP, Roche Diagnostics Corporation, IN, USA). The troponin detection limit was 0.01ug/L for cohort 1 and 5ng/L for cohort 2 because a high sensitivity troponin assay was introduced between the cohorts (troponin and TnT-hs, Roche Diagnostics Corporation).

NT-proBNP >220pmol/L and troponin T >0.03μg/L in cohort 1 and >50ng/L in cohort 2 are considered abnormal according to local laboratory reference values. These levels were used

to group participants into normal cardiac biomarkers, high troponin T only, high NT-proBNP only and both high troponin T and NT-proBNP groups (figure 1).

Statistical analysis

The primary end point was survival after discharge. Patients who died during their index admission were excluded from the analyses. This was plotted using Kaplan-Meier survival curves for the groups with normal or abnormal biomarkers. Cox proportional hazard ratios (HR) were calculated with and without adjustment for acute COPD severity using the CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, Age ≥65) score and acidaemia (blood pH <7.30) on admission, and severity of airflow obstruction using FEV_1% of predicted[10, 12]. Secondary end-points were readmissions for exacerbations of COPD or acute cardiac disease. Because patients may have died before readmission, these were calculated as COPD admission-free survival and cardiac admission-free survival respectively, with follow-up censored at the date of death. Because these analyses used pre-existing cohorts, no formal sample size calculations were undertaken. Analyses were conducted with Stata (v.16, College Station, TX)

Results:

The contribution of each cohort is shown in (figure 1). The demographic and clinical characteristics of the participants are shown in (table 1). Detailed baseline characteristics have been published previously[10, 11], and are available in supplement tables 1 and 2. Including those who died during the index admission, 7%, 33% and 61% of patients died in the first 30 days, 2 years and 5 years respectively (figure 2). Risk factors for death at 5 years after index admission are shown in supplement table 3 and these include a history of cardiac disease recorded at the time of the index admission.

Kaplan Meier survival curves for those who survived to discharge from the index admission (n=384) for each cardiac biomarker group are shown in (figure 2). Visual inspection indicated that the proportional hazards assumption was met and the Cox proportional HRs are shown in table 2. Compared to participants who had normal cardiac biomarker measurements, participants with elevated NT-proBNP only had 2.13 times higher mortality during this period. This remained the case after adjusting for exacerbation severity (acidaemia and CURB-65), and baseline lung function (FEV_1% of predicted) (table 2). By contrast elevated troponin T only was not associated with a worse 5-year survival compared to those with normal biomarkers and participants with abnormalities of both NT-proBNP and troponin T had similar survival to those who only had abnormal NT-proBNP (figure 2, table 2). These findings were similar after adjusting for a history of cardiac disease (supplement table 4).

Cardiac biomarkers were not associated with future COPD exacerbations (figure 3). However, compared to participants who had normal cardiac biomarker measurements, participants with elevated NT-proBNP alone or both elevated NT-proBNP and troponin T were more likely to be admitted for cardiac disease within 5 years (figure 4). Elevated troponin T alone was not associated with future cardiac admissions.

Discussion:

We have found that an elevated NT-proBNP is a strong predictor of poor long-term prognosis among patients admitted to hospital with an exacerbation of COPD. The overall mortality rate was nearly twice as high among those with elevated NT-proBNP even after adjusting for lung function and exacerbation severity (figure 2, table 2). Elevated troponin T, however, did not predict long-term mortality. These findings suggest that subclinical cardiac dysfunction, but not necessarily acute cardiac injury, is an important determinant of long-term mortality in the setting of COPD exacerbations.

We have previously reported that elevated levels of NT-proBNP and troponin T and their combination were associated with a high short-term (30 day) mortality in cohort 1[10]. In that analysis we did not find that either biomarker was associated with subsequent survival between 30 days and one year. This new analysis extends these findings by combining data from two prospective cohorts with much longer follow up. The findings show that elevated NT-proBNP is strongly associated with both short- and long-term prognosis after an exacerbation of COPD. NT-proBNP is released by the myocardium as a result of myocardial stretch and is a sensitive indicator of cardiac failure[15]. We also found that high levels of NT-proBNP predicted future admissions for cardiac disease, but not future COPD admissions (figures 3 and 4). Hence, subclinical evidence of cardiac dysfunction at the time of an exacerbation may indicate poor cardiac reserve and be a harbinger of future cardiac events. Cardiac dysfunction did not predict acute COPD exacerbations suggesting that poor cardiac reserve may not be an aetiologic factor in COPD exacerbations.

In the previous analyses of these cohorts[10, 12], a history of cardiac disease was not a predictor of 30-day or 1-year mortality. However, an analysis of this combined cohort show that a history of cardiac disease and treatment with cardiac medications (notably diuretics) were associated with higher long-term mortality at 5 years (supplement table 3). The associations of the biomarkers with five-year survival remained similar after adjustment for a history of cardiac disease, suggesting that findings that acute cardiac dysfunction during exacerbations of COPD is associated with a poor long-term prognosis independently of a known cardiac disease.

While Troponin T levels on admission were associated with short-term mortality in these cohorts, and have been linked to worse prognosis in other studies they did not predict long-term mortality, nor did they predict future cardiac admissions in these cohorts[4, 16]. Cardiac troponins form part of the diagnosis of myocardial infarction, but are sensitive markers of myocardial injury of any cause, including acute compromise of the pulmonary circulation[15-17]. Our observation that troponin is associated with short-term but not long-term mortality is probably best explained by troponins being released as a consequence of the acute COPD exacerbation causing transient cardiac myocyte injury, but this does not necessarily reflect clinically important underlying cardiac disease. There was no evidence that the raised levels of troponin T were caused by acute coronary syndromes in the study: those with clinically suspected acute coronary syndromes were excluded and there was little electrocardiographic evidence of cardiac ischaemia. Having a raised troponin level does not necessarily mean an acute coronary syndrome, even among those with a known history of coronary artery disease, as the diagnosis requires a compatible clinical history, serial changes of troponin, and dynamic electrocardiographic changes. Most patients with raised troponins do not have sufficient evidence to support the diagnosis of acute coronary syndrome[18], and we have previously shown that ECG and chest x-rays often do not detect

subclinical biomarker derangements[13]. An additional analysis of these cohorts also revealed that a history of cardiac disease was not associated with a high troponin level on admission (OR 1.22, 95% CI (0.69-2.14) p=0.499).

There is no universally accepted biological mechanism linking COPD and heart disease although there are several plausible explanations. COPD and cardiac disease share many risk factors such as smoking, older age and a chronic inflammatory state[19]. COPD is associated with atherosclerosis and arterial stiffness[20, 21], which increase the risk of cardiac ischaemia[22]. COPD exacerbations are associated with elevated systemic inflammatory markers such as C-reactive protein, interleukin-6, and platelet activation, which are also linked to atherosclerosis[23-26]. Our findings suggest that while an acute insult (i.e. the index admission for COPD) may lead to a troponin rise, only those with cardiac remodelling and reduced cardiac reserve indicated by a high NT-proBNP have a worse long-term prognosis .

Exacerbations of COPD are known to increase systemic sympathetic tone leading to higher metabolic demands of tissues and increasing the risk of cardiac ischaemia[27]. Furthermore, severe exacerbations of COPD are usually treated with high doses of β-2 agonists, which stimulate cardiac β-2 receptors leading to increases in heart rate[28], and increasing cardiac stress.

Lung hyper-inflation caused by COPD is associated with reduced cardiac exercise tolerance so could contribute to cardiac co-morbidity in COPD patients[29]. Pulmonary hypertension is estimated to affect around 30% of patients with moderate and severe COPD[30], causing right ventricular dilatation and hypertrophy, leading to restriction of the left ventricle resulting in a lower cardiac output[31].

Many of these inflammatory and physiological mechanisms are likely to worsen during exacerbations of COPD. We have previously found that NT-proBNP continues to rise during the first few days of a COPD exacerbation, but falls as the patient recovers a few weeks later[11]. Whether NT-proBNP during stable COPD is an indicator of long-term prognosis is not yet known[32]. As up to half of COPD patients have left ventricular dysfunction, further investigations into this biochemical marker of cardiac overload may provide valuable insights into the complex interplay of heart-lung pathophysiology[33-35].

A major strength of this study is that these are large, unselected, prospectively-recruited cohorts of patients with exacerbations of COPD, with near-complete follow-up data. The outcomes were objective (mortality or readmission). We were also able to adjust for confounders by the severity of the exacerbation and lung function impairment in the analyses. A limitation is that both cohorts are from a single centre, however, this reduces the potential for confounding. The overall 5-year mortality of 61% is similar to other cohorts[4], suggesting that our findings are likely to be generalisable to other centres.

There were some differences between the cohorts: cohort 2 was smaller and excluded patients with severe renal disease or terminal malignancy meaning that patients recruited into cohort 2 were healthier than cohort 1. Participants in cohort 2 were less likely to die in 5-years (HR=0.71 (95% CI 0.54-0.93), p=0.013,) but there was no difference between cohorts once adjusted for CURB65, pH, and FEV_1% of predicted (adjusted HR 0.95 (95% CI 0.70-1.29)

p=0.75). The findings were similar for each cohort if analysed separately, hence it seems reasonable to combine the cohorts for the ease of interpretation. In both cohorts, the patients were treated according to best practice at time of admission and participation in these studies did not influence treatment. The absolute number of patients with elevated biomarkers is also low which might influence the results of analyses in particular of troponins. Other limitations of this study include the possibility that some readmissions were not included in the electronic database if these occurred outside the Waikato region, although all deaths are recorded regardless of where they occurred. Another limitation is that although cardiac medications on admission were recorded, data on subsequent cardiac medications received during the follow-up period were not. Therefore, we were unable to analyse the impact of cardiac medications on long-term outcomes following an exacerbation of COPD. The frequency of COPD exacerbations before index admission was also not collected and therefore was not accounted for in the analyses. A further limitation is that the treating clinicians were not blinded to the results of the cardiac biomarkers and that this information may have influenced their diagnosis of acute cardiac disease and management. This might be expected to reduce the association between biomarkers and mortality, but it is possible that knowledge of a previously abnormal NT-proBNP influenced clinicians to diagnose future events as being of cardiac origin, inflating the association between NT-proBNP and cardiac admissions. The exact causes of death were also not available and we were unable to analyse if they differ between biomarker groups.

These findings highlight the critical importance of cardiac co-morbidity in COPD. This may be even more important at the time of a COPD exacerbation, but may not be recognised. Clinicians should be aware of this and carefully look for cardiac involvement. Whether early diagnosis and treatment of cardiac disease in patients with COPD could improve both long- and short-term outcome is unproven, but identifying subclinical cardiac disease will likely help the assessment of prognosis. Future research is needed to better characterise the relationship and understand the mechanisms of cardiac dysfunction in COPD. It would be of particular interest to determine whether cardiac dysfunction is the cause of higher mortality in COPD or whether it is simply a marker of more severe COPD. Our finding that cardiac dysfunction during a COPD exacerbation is associated with future cardiac admissions but not future COPD admissions signals that treatments targeting cardiac dysfunction may improve outcomes in this population by reducing cardiac rather than respiratory events.

In summary, exacerbations of COPD have a poor long-term prognosis with more than half of patients dying within 5 years of hospitalisation. Abnormal levels of NT-proBNP, a marker of cardiac stretch and cardiac failure, at the time of the COPD admission are associated with higher long-term mortality and subsequent admissions for cardiac disease.

Table 1: Baseline characteristics. Mortality data excluded 8 patients who did not have both cardiac biomarkers measured on admission.

|	N	
Age (years)	409	70.1 (69-71.2)
BMI (kg/m^2)	401	24.6 (23.9-25.2)
Current smoker	409	126 (31%)
FEV$_1$ (L)	404	0.79 (0.76-0.83)
FEV$_1$ (% predicted)	404	34.7 (33.3-36.2)
Acidaemia (blood pH <7.30)	364	56 (15%)
PaCO2 (mmHg)	315	47.9 (46.3-49.7)
PaO2 (mmHg)	312	63.8 (61.5-66.2)
History of cardiac disease	409	152 (37%)
History of malignancy	409	42 (10%)
Cardiac medication on admission		
Beta-blocker	409	45 (11%)
Calcium-channel blocker	409	97 (24%)
Angiotensin converting enzyme inhibitor / Angiotensin receptor blocker	409	158 (39%)
Diuretic	409	152 (37%)
Antiplatelet	409	159 (39%)
Anticoagulation	409	28 (7%)
Statin	409	116 (28%)
Cardiac biomarker levels at presentation		
NT-proBNP (pmol/L)	405	62.5 (53.7-72.7)
Troponin T Cohort 1 (ug/L) Cohort 2 (ng/L)	239 162	0.015 (0.014-0.017) 18.3 (16.2-20.7)
Mortality		
In-hospital	401	17 (4%)
30-day	401	29 (7%)
1-year	401	82 (20%)
2-year	401	133 (33%)
5-year	401	245 (61%)

Continuous data are presented in geometric mean and confidence interval. Categorical data are presented in frequency and percentage.

BMI = body mass index, CI = confidence interval, FEV1 = forced expiratory volume in 1s, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PaCO2 = arterial partial pressure of carbon dioxide, PaO2 = arterial partial pressure of oxygen
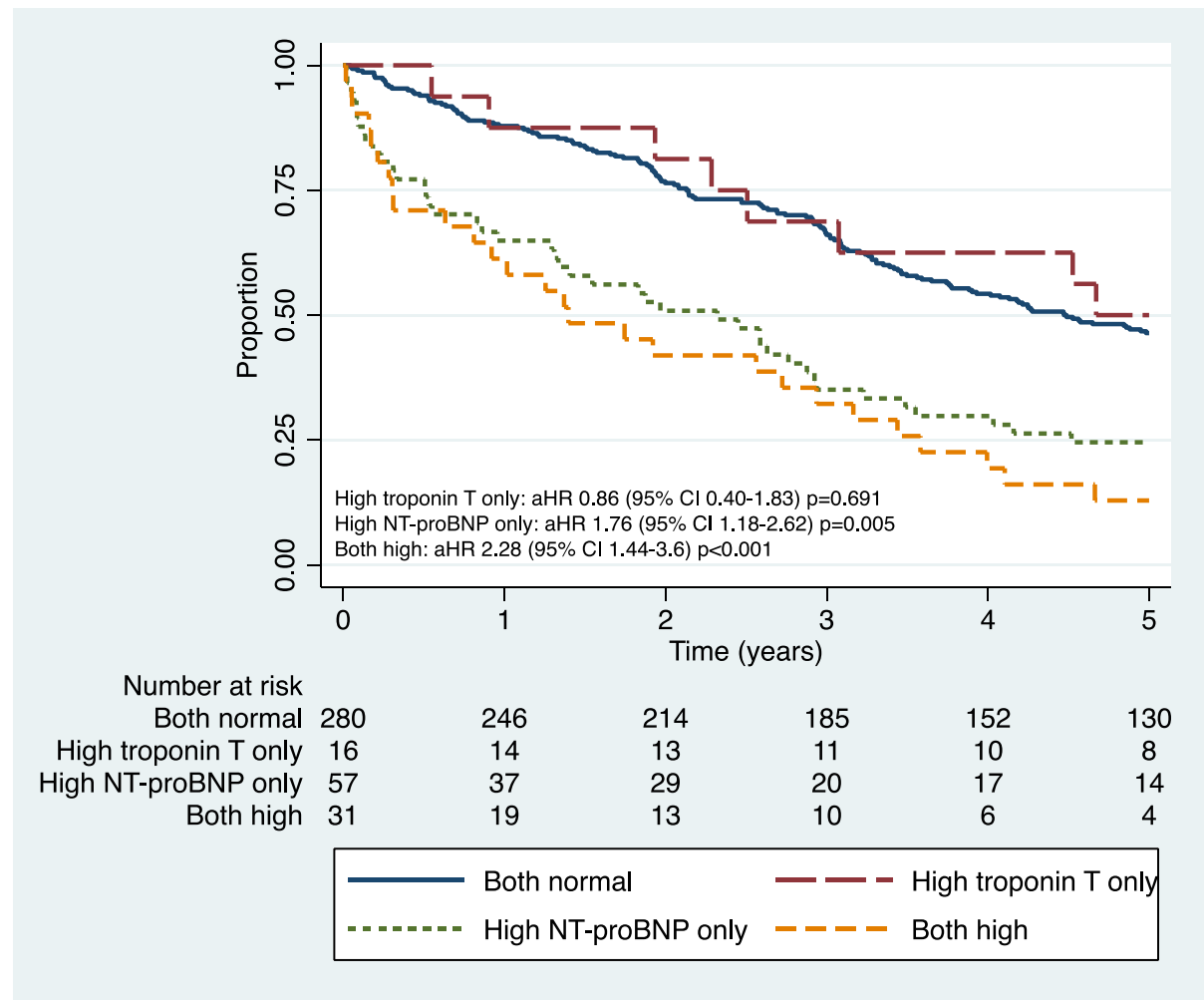
Table 2: Combined cohort adjusted and unadjusted hazard ratios for five year survival, exacerbation free survival and cardiac admission free survival following discharge after index COPD admission according to cardiac biomarker status. HR = Hazard ratio, CI = confidence interval. HR adjusted for CURB65, acidaemia (pH<7.30), and FEV_1% of predicted.

	Unadjusted				Adjusted			
	n	HR	95% CI	p-value	n	HR	95% CI	p-value
Survival	384				337			
- High troponin T only		0.89	0.43-1.80	0.738		0.86	0.40 – 1.83	0.691
- High NT-proBNP only		2.13	1.52-2.99	<0.001		1.76	1.18-2.62	0.005
- Both high		2.82	1.87-4.26	<0.001		2.28	1.44-3.60	<0.001
Exacerbation free survival	384				337			
- High troponin T only		1.03	0.60-1.77	0.906		0.91	0.49-1.66	0.753
- High NT-proBNP only		1.17	0.86-1.58	0.320		1.10	0.78-1.54	0.603
- Both high		1.29	0.88-1.89	0.196		1.27	0.83-1.95	0.277
Cardiac admission free survival	384				337			
- High troponin T only		0.87	0.44-1.70	0.681		0.74	0.34-1.57	0.431
- High NT-proBNP only		2.13	1.54-2.95	<0.001		1.75	1.20-2.55	0.003
- Both high		2.55	1.70-3.84	<0.001		1.98	1.25-3.12	0.003

Figure 1: study design. Patients who died in hospital (n=17) were included in overall mortality data but were excluded from survival analyses after discharge.
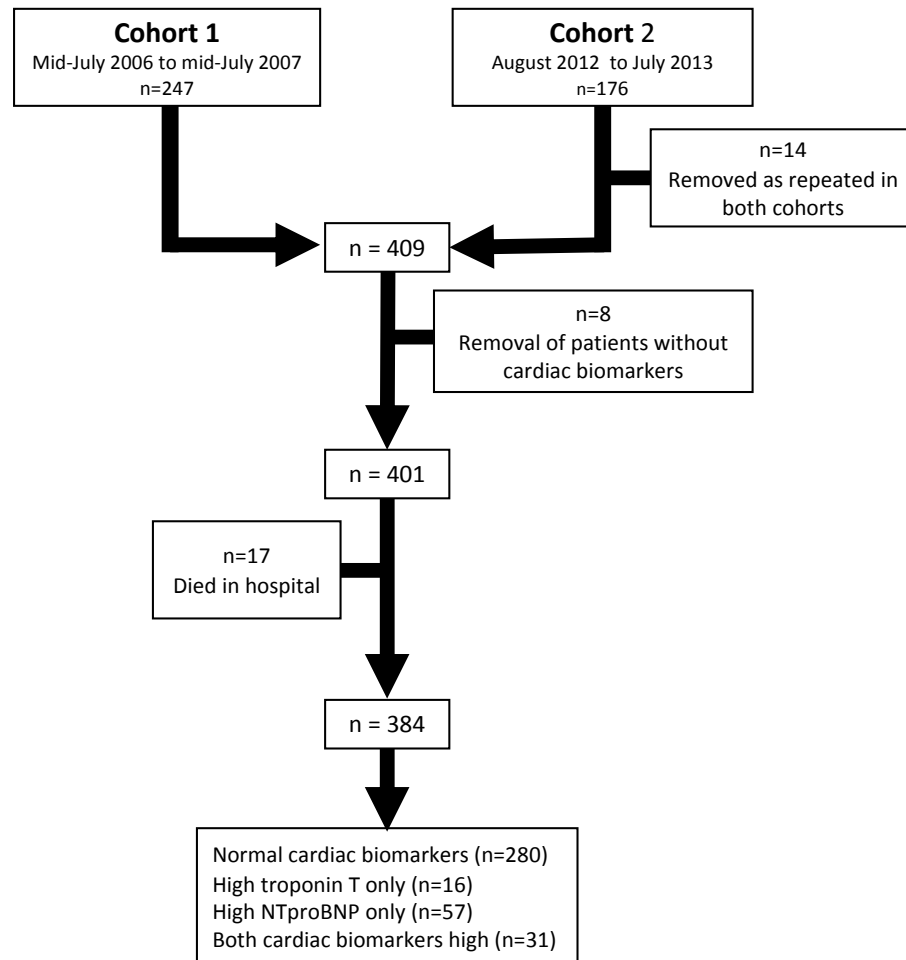
Figure 2: Kaplan-Meier curve of survival over 5 years after discharge for exacerbation of COPD. HR adjusted for CURB-65, acidaemia (pH<7.30) and FEV_1 % of predicted. aHR = adjusted Hazard ratio, CI = confidence interval.

High troponin T only: aHR 0.86 (95% CI 0.40-1.83) p=0.691
High NT-proBNP only: aHR 1.76 (95% CI 1.18-2.62) p=0.005
Both high: aHR 2.28 (95% CI 1.44-3.6) p<0.001

Number at risk						
Both normal	280	246	214	185	152	130
High troponin T only	16	14	13	11	10	8
High NT-proBNP only	57	37	29	20	17	14
Both high	31	19	13	10	6	4

Figure 3: Kaplan-Meier curve of subsequent COPD hospitalisations following discharge after index COPD exacerbation. HR adjusted for CURB65, acidaemia (pH<7.30) and FEV_1 % of predicted. aHR = adjusted Hazard ratio, CI = confidence interval.
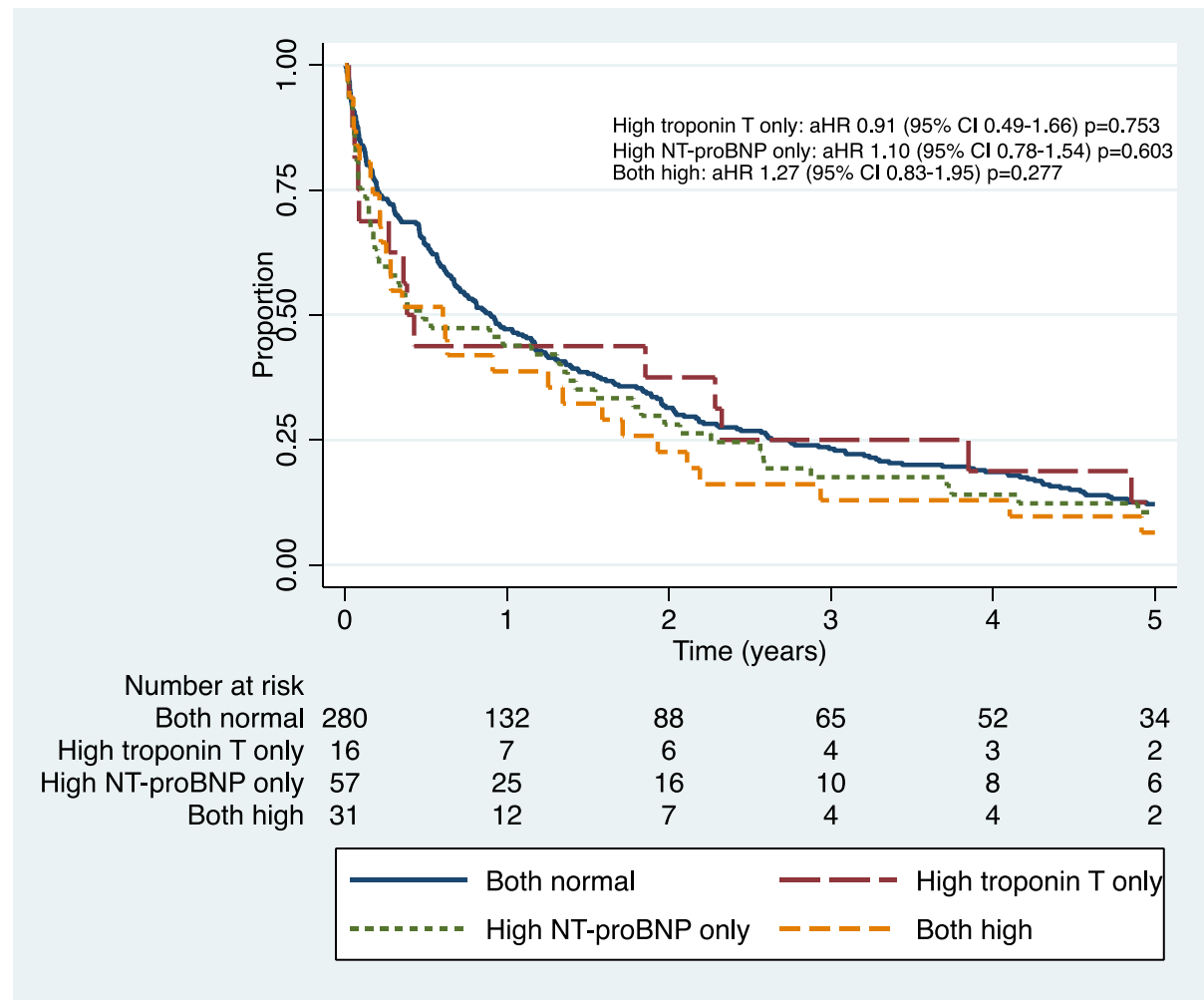
Figure 4: Kaplan-Meier curve of subsequent cardiac hospitalisations over 5 years following discharge after index COPD exacerbation. HR adjusted for CURB65, acidaemia (pH<7.30) and FEV_1 % of predicted. aHR = adjusted Hazard ratio, CI = confidence interval.
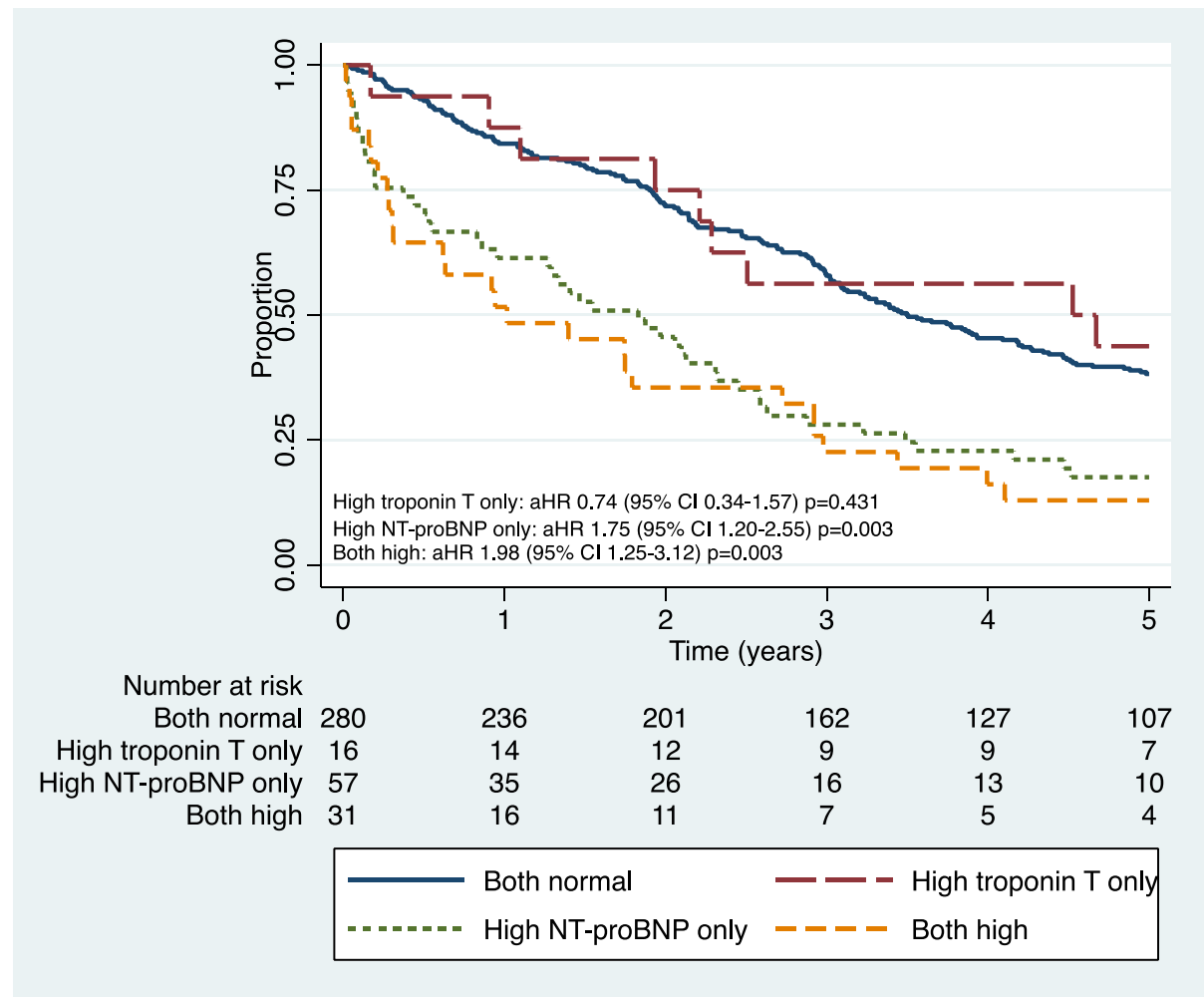
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Supplement Table 1: Characteristics of patients in cohort 1

Variable	
Number of patients, n	247
Female, n (%)	138 (56)
Ethnicity, n (%)	
New Zealand European	201 (81)
Maori / Other	46 (19)
Age, mean in years (SD)	72.2 (10.6)
Smoking status, n (%)	
Current smoker	66 (27)
Ex-smoker	172 (70)
Never	9 (3)
Post-bronchodilator spirometry, mean (SD)	
FEV_1 (litres)	0.80 (0.33)
FEV_1 (% predicted)*	36 (15)
COPD Severity, n (%)	
Mild (FEV_1 % predicted >80)	1 (0.4)
Moderate (FEV_1 % predicted 50-79)	41 (16.9)
Severe (FEV_1 % predicted 30-49)	108 (44.4)
Very Severe (FEV_1 % predicted <30)	93 (38.3)
COPD treatment pre-admission, n (%)	
Inhaled long-acting beta-agonist ± inhaled corticosteroid	111 (45)
Inhaled long-acting anti-muscarinic	63 (26)
Long-term oxygen therapy	74 (30)
BMI – mean in kg/m^2 (SD)	25.2 (6.2)
Comorbidities, n (%)	
Chronic kidney disease	21 (9)
Malignancy	22 (9)
Cardiac disease	74 (30)
Cerebrovascular disease	28 (11)
Liver disease	2 (1)
None of the above	141 (57)
CURB-65 score, n (%)	
0-1	89 (36)
2-3	138 (56)
4-5	20 (8)
Blood gases, n (%)	
pH <7.30	40 (17)
$PaCO_2$ >45 mmHg	113 (48)
PaO_2 <60 mmHg	105 (45)
Treatment, n (%)	
Systemic corticosteroids	243 (98)
Antimicrobial therapy	238 (96)
Bronchodilator	246 (99)
Intravenous fluids	61 (25)
Non-invasive ventilation	24 (10)
Ventilation via endotracheal tube	2 (1)
Intensive/high dependency care admission	16 (6)

BMI = body mass index, COPD = chronic obstructive pulmonary disease, CURB-65 = (confusion, urea >7 mmol/L, respiratory rate ≥30/min, <90 mmHg systolic or <60 mmHg diastolic blood pressure, age ≥65 years), FEV_1 = forced expiratory volume in

one second, $PaCO_2$ = arterial partial pressure of carbon dioxide, PaO_2 = arterial partial pressure of oxygen, SD = standard deviation.

*European Respiratory Society recommended reference equations

Supplement Table 2: Characteristics of patients in cohort 2

Variable	
Number of patients, n	176
Female, n (%)	95 (54)
Ethnicity, n (%) New Zealand European Maori / Other	 127 (72) 49 (28)
Age, mean in years (SD)	69.5 (10.4)
Smoking status, n (%) Current smoker Ex-smoker	 60 (34) 116 (66)
BMI (kg/m^2), mean (SD)	25.6 (7.9)
Post-bronchodilator spirometry, mean (SD) FEV$_1$ (litres) FEV$_1$ (% predicted)*	 0.95 (0.4) 39.3 (16.5)
COPD Severity, n (%) Mild (FEV$_1$ % predicted >80) Moderate (FEV$_1$ % predicted 50-79) Severe (FEV$_1$ % predicted 30-49) Very Severe (FEV$_1$ % predicted <30)	 3 (1.7) 42 (24) 76 (43) 55 (31)
MRC dyspnoea scale prior to exacerbation, n (%) 1-2 3 4 5	 16 (9) 17 (10) 39 (22) 104 (59)
St. George's Respiratory Questionnaire COPD score, mean (SD) Symptoms component Activity component Impacts component Total score	 35 (10) 85 (19) 54 (20) 56 (14)
COPD treatment pre-admission, n (%) Inhaled long-acting beta-agonist ± inhaled corticosteroid Inhaled long-acting anti-muscarinic Long-term oxygen therapy	 123 (70) 107 (61) 19 (11)
Comorbidities, n (%): Cardiac disease Ischemic heart disease Heart failure Atrial fibrillation / flutter Peripheral vascular disease Cerebrovascular disease Malignancy Hypertension Dyslipidaemia Diabetes Chronic kidney disease Obesity (BMI>30) Obstructive sleep apnoea	 74 (42) 37 (21) 33 (19) 33 (19) 15 (9) 15 (9) 21 (12) 84 (48) 44 (25) 24 (14) 6 (3) 40 (23) 7 (4)
Charlson Comorbidity Index, n (%) 1-2	 122 (69)

Variable	
3-4	46 (26)
5-7	8 (5)
CURB-65 score, n (%)	
0-1	108 (61)
2-3	65 (37)
4-5	3 (2)
Blood gases, n (%)	
pH <7.30	16 (12)
PaCO$_2$ >45 mmHg	45 (54)
PaO$_2$ <60 mmHg	38 (47)
Treatment received, n (%)	
Systemic corticosteroids	174 (99)
Antimicrobial therapy	164 (93)
Oxygen therapy	109 (62)
Nebulised bronchodilator	77 (43)
Intravenous fluids	44 (25)
Furosemide	23 (13)
Non-invasive ventilation	22 (13)
Ventilation via endotracheal tube	2 (1)
Intensive/high dependency care admission	16 (9)

BMI = body mass index, COPD = chronic obstructive pulmonary disease, CURB-65 = (confusion, urea >7 mmol/L, respiratory rate ≥30/min, <90 mmHg systolic or <60 mmHg diastolic blood pressure, age ≥65 years), FEV$_1$ = forced expiratory volume in one second, MRC = medical research council, PaCO$_2$ = arterial partial pressure of carbon dioxide, PaO$_2$ = arterial partial pressure of oxygen, SD = standard deviation.

*National Health and Nutrition Examination Survey (NHANES III) reference equations

Supplement Table 3: Univariate logistic regression analyses of risk factors for death at 5 years in patients hospitalised for acute exacerbation of COPD

Variable	n/N	5-year mortality		
		OR	95% CI	p-value
Age (in years)	409	1.06	1.04-1.09	<0.001
BMI (kg/m^2)	401	0.95	0.92-0.98	0.001
Current smoker	126/409	0.51	0.33-0.77	0.002
CURB-65	409	1.48	1.22-1.79	<0.001
Acidaemia (pH<7.30)	56/364	2.91	1.44-5.84	0.003
FEV1 % predicted	404	0.99	0.97-0.99	0.024
Cardiac disease	152/409	2.26	1.47-3.48	<0.001
Cardiac medications	310/409	2.15	1.36-3.41	0.001
Beta-blocker	45/409	0.58	0.31-1.09	0.09
Calcium channel blocker	97/409	1.52	0.94-2.46	0.089
ACE inhibitor / Angiotension receptor blocker	158/409	1.31	0.87-1.98	0.198
Diuretics	152/409	2.37	1.54-3.66	<0.001
Antiplatelet	159/409	1.17	0.78-1.75	0.456
Anticoagulation	28/409	1.40	0.62-3.18	0.420
Statins	116/409	0.93	0.60-1.45	0.764
High NT-proBNP	98/405	3.73	2.13-6.51	<0.001
High troponin T	58/401	2.77	1.42-5.42	0.003

BMI = body mass index, CURB-65 = (confusion, urea >7 mmol/L, respiratory rate ≥30/min, <90 mmHg systolic or <60 mmHg diastolic blood pressure, age ≥65 years), FEV_1 = forced expiratory volume in one second, ACE = angiotensin converting enzyme.

Supplement Table 4: Five-year survival analysis of survivors of index admission (n=337) adjusted for CURB-65, acidaemia (pH<7.30), FEV_1% of predicted, and history of cardiac disease.

	Adjusted (CURB-65, acidaemia, FEV1% and cardiac disease)		
	HR	95% CI	p-value
Survival			
- High troponin only	0.87	0.41-1.87	0.732
- High NT-proBNP only	1.72	1.15-2.55	0.008
- Both high	2.44	1.54-3.87	<0.001

CURB-65 = (confusion, urea >7 mmol/L, respiratory rate ≥30/min, <90 mmHg systolic or <60 mmHg diastolic blood pressure, age ≥65 years), FEV_1 = forced expiratory volume in one second, HR = Hazard ratio, CI = confidence interval.