Original Article

Prevalence and impact of non-cardiovascular comorbidities among older adults hospitalized for non-ST segment elevation acute coronary syndrome

Richard Ofori-Asenso[1,2,3], Ella Zomer[1], Ken Lee Chin[1], Peter Markey[4], Si Si[1], Zanfina Ademi[1], Andrea J. Curtis[3], Sophia Zoungas[3], Danny Liew[1]

[1]Centre of Cardiovascular Research and Education in Therapeutics, [2]Epidemiological Modelling Unit, [3]Division of Metabolism, Ageing and Genomics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; [4]Alfred Hospital, Melbourne, Victoria, Australia

Contributions: (I) Conception and design: R Ofori-Asenso, D Liew, E Zomer; (II) Administrative support: None; (III) Provision of study material or patients: None; (IV) Collection and assembly of data: R Ofori-Asenso, D Liew, E Zomer, P Markey; (V) Data analysis and interpretation: R Ofori-Asenso; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor Danny Liew. Department of Epidemiology and Preventive Medicine, Monash University, 553, St Kilda Road, Melbourne, VIC 3004, Australia. Email: danny.liew@monash.edu.

Background: There is a paucity of information on the prognostic importance of non-cardiovascular comorbidities (NCCs) among patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). This study examined the prevalence and impact of NCCs on the length of stay (LOS) and mortality among older adults hospitalized for NSTE-ACS.

Methods: Among 1,488 older adults (mean age 79.4±8.4 years; 62.0% male) hospitalized for NSTE-ACS at a tertiary hospital in Melbourne, Australia, during 2013–2015, we collected data on comorbidities, LOS, and discharge outcomes. Thirteen NCCs were studied. Negative binomial and Cox proportional regression models were applied to examine the association between NCCs and LOS and in-hospital death, respectively.

Results: Approximately 53% of the patients had ≥1 NCCs. Diabetes and renal disease as well as anemia and renal disease co-existed more frequently than expected. Compared to having no NCCs, having one NCC was not associated with a significant increase in the likelihood of longer LOS [incidence rate ratio (IRR) 1.07; 95% CI: 0.99–1.15; P=0.085] or in-hospital death [hazard ratio (HR) 1.11; 95% CI: 0.65–1.90; P=0.707]. However, having ≥2 NCCs was associated with 22% and 79% increased likelihood of longer LOS (IRR 1.22, 95% CI: 1.11–1.33; P<0.001) and in-hospital death (HR 1.79, 95% CI: 1.06–3.03; P=0.029), respectively, compared to not having any NCC. Certain NCC dyads [e.g., chronic pulmonary disease (CPD) + renal disease] exhibited multiplicative effect such that their impact on patients' LOS or survival exceeded the sum of the individual effects of the component NCCs.

Conclusions: Over half of older patients hospitalized with NSTE-ACS had NCCs. A higher burden of NCCs correlated with increased LOS and lower survival. Contemporary ACS management guidelines need to recognize and incorporate protocols for the treatment of individuals with multiple chronic conditions to reduce the occurrence of adverse outcomes.

Keywords: Acute coronary syndrome (ACS); myocardial infarction; hospitalization; comorbidity; multimorbidity

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Introduction

Coronary artery disease (CAD) is a leading cause of global morbidity and mortality (1,2). Its acute (and most ominous) manifestation, acute coronary syndrome (ACS), is associated with >2.5 million hospitalizations annually worldwide (3). Unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI) share similar clinical presentations, but differ in severity and are collectively referred to as non-ST elevation ACS (NSTE-ACS). Together, they account for over 60% of ACS cases (4,5).

The risk of ACS increases with age and the co-existence of risk factors such as hypertension and smoking (4,6,7). In Australia, the recorded cases of ACS increased by 79% from 1993 to 2008 for acute myocardial infarction (AMI) and 33% for UA, resulting in over 90,000 hospitalizations in 2008 (8). More than 8,000 Australians died from AMI in 2016, among whom over 80% were aged 65 years and over (9). In 2009, the direct healthcare costs associated with ACS in Australia exceeded AUD $1.8 billion (10).

ACS clinical guidelines are largely based on trials in which the elderly and people with comorbidities were under-represented (11,12). However, the majority of ACS patients seen in routine clinical practice are likely to belong to this group. In Sweden, around half of cardiologists reported treating elderly NSTE-ACS patients with multimorbidity daily (13). Approximately 60% of patients with ACS in England and Wales were found to have multimorbidity (14). One in every 3 patients hospitalized for ACS in Switzerland had two or more other cardiovascular conditions (15). In Australia, similar patterns are observed (16,17).

To optimize the clinical management of patients with ACS, better knowledge of the impact of comorbidities is vital (18,19). Prior studies that have utilized comorbidity indices such as the Charlson comorbidity index (CCI) and the CAD-specific comorbidity index have associated higher global comorbidity with poorer outcomes among patients with ACS (20,21). However, the extent of, and the impact of NCCs on outcomes experienced by ACS patients has not been well studied. Defining the burden of and the effect of NCCs among ACS patients might help to raise awareness about the clinical relevance of NCCs among clinicians which could improve the assessment of patients' vulnerability, and also inform decision making about the care delivered to such patients.

In this study, we sought to characterize the patterns and impact of NCCs on the length of stay (LOS) and mortality among older adults hospitalized for NSTE-ACS.

Methods

Study design and patient selection

This was a retrospective study which utilized administrative data from the Alfred Hospital, a major tertiary hospital in Melbourne, Australia. We assembled a cohort of all consecutive adults aged 65 years and over, who were hospitalized for NSTE-ACS between July 2013 and December 2015. NSTE-ACS was defined by the International Classification of Diseases, Version 10, Australian Modification (ICD-10-AM) codes (22). The relevant NSTE-ACS codes were I21.4 (NSTEMI) and I21.0 (UA). Patients were eligible for inclusion if at least one of the above codes was listed as a primary reason (diagnosis) for their admission.

Non-cardiovascular comorbidities (NCCs)

The CCI has been widely used in clinical research to address the confounding effect of comorbidities, predict outcomes, as well as to standardize comorbidities abstracted from medical records or administrative databases (20,23,24). The CCI incorporates 17 comorbidities that were originally evaluated for their prognostic impact on 1-year mortality risk (24). To determine a set of relevant NCCs to examine in our study, we selected a priori those NCCs incorporated in the CCI—dementia, chronic pulmonary disease (CPD), connective tissue disorders (CTD), peptic ulcer disease, diabetes mellitus, liver disease, malignancy, HIV and renal disease. This approach to selecting NCCs has previously being adopted by other studies that have examined the impact of NCCs on hospitalisation outcomes (25). In addition, while not included in the CCI, we added anemia, depression and psychoses because prior studies have identified these as significant prognostic factors in ACS patients (26,27). Furthermore, we included obesity given its growing public health burden (28). *Table S1* provides the relevant codes used for ascertaining various comorbidities.

Outcomes

We examined LOS and in-hospital mortality among the study cohort. In-hospital fatality rate was calculated as the ratio of the number of cases ending in death (from any cause) to the total number of cases. LOS was calculated as the period from the time of admission to the time of

separation (death or discharged alive).

Covariates

For each patient, we collected demographic data on date of birth, sex, place of birth, postcode of residence, marital status and whether or not the patient identified as an Aboriginal and/or Torres Strait Islander. Postcode of residence was used to describe socioeconomic status as per the Australian Bureau of Statistics' Socio-Economic Indices for Areas (SEIFA) and the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) (29). The IRSAD is a general socioeconomic index that summarizes a range of information about the economic and social conditions of people and households within an area. Clinical data included the type of NSTE-ACS, information on coronary interventional procedures [e.g., coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI)], admission to intensive care unit (ICU), and presence or absence of any complications during hospital stay. Information regarding smoking, hypertension and atrial fibrillation (AF), and other comorbidities that are captured in the CCI were also collected.

Statistical analyses

Descriptive statistics were used to summarize baseline characteristics. Variables were compared across patients with differing levels of NCCs using the χ^2 test for proportions, one-way analysis of variance (ANOVA) for means and Kruskal-Wallis rank test for the comparison of medians. The prevalence of each of the 13 NCCs was calculated as the ratio of the patients with that comorbidity to the overall number of NSTE-ACS patients. The occurrence of NCC dyads was examined by clustering the individual conditions per patient and estimating the prevalence for each combination with a focus on the five most prevalent dyads. The expected (E) prevalence of each dyad was calculated by multiplying the total prevalence of the single NCC within the dyad by each other (e.g., for NCC dyad XY, the expected prevalence would be prevalence of comorbid X × prevalence of comorbid Y) (17,30). The observed (O) and expected (E) prevalence of each NCC dyad were compared via a two-sample test of proportion (31).

We performed three different analyses. In the first, individual NCCs were considered as exposures. In the second analysis, the exposure was considered as the cumulative number of NCCs and the patients were classified into three groups based on having 0, 1 and ≥2 NCCs. In the third set of analyses, the occurrence of NCC dyads was considered as the exposure whereby for each dyad, patients were grouped into whether they had none, only one or both of the component NCCs. For example, for dyad XY, patients would be grouped into: (I) with neither X nor Y; (II) with X but not Y; (III) with Y but not X; (IV) with both X and Y.

The associations between NCCs and LOS and in-hospital mortality were examined by means of a negative binomial regression (NBR) model and Cox proportional hazards regression model, respectively. Backward stepwise approach was applied to select covariates (from the possible list in *Table 1*) in multivariable NBR and Cox models with removal set at probability of 0.20 (25). The exposure of interests was forced into the respective models. Assessments of model fit, collinearity and interactions were performed. Survival patterns were depicted by Kaplan-Meier curves. The log-rank test was used to compare the survival between ties. Unless otherwise specified, a priori statistical significance was set at $P<0.05$. All analyses were performed with STATA (version 15/1C, Stata Corp, College Station, Texas, USA).

Ethics approval

The study received approval from the Alfred Hospital Human Research Ethics Committee (project number 146/17).

Results

Cohort characteristics

A total of 1,488 older adults were included in the analysis, of whom 77.1% and 22.9% were hospitalized for NSTEMI and UA, respectively. The mean age of the cohort was 79.4 (SD 8.4) years and 62.0% were males. Approximately 2.4% were patients from an aged care residential facility. Over half (56.9%) of the patients were born overseas and 11.4% were non-English speaking and required an interpreter. A total of 26.4%, 60.9%, 25.4%, 3.9%, 2.2% and 3.1% patients had AF, hypertension, chronic heart failure, cerebrovascular disease, peripheral vascular disease and currently smoked, respectively. Nearly 1 in 8 (12.8%) had a previous history of CABG and a quarter (24.5%) with PCI. One in five (20.6%) patients were admitted to the ICU. Overall, 31.9% had only one NCC, whereas 20.9%

Table 1 Sociodemographic and clinical characteristics of older adults hospitalized for non-ST-elevation acute coronary syndrome (NSTE-ACS)

Variables	All (n=1,488)	Number of non-cardiovascular comorbidities*			P value†
		0 (n=703)	1 (n=474)	≥2 (n=311)	
Mean age, years (SD)	79.4 (8.4)	78.8 (8.9)	79.7 (7.8)	80.3 (8.0)	0.0169
≥85 years, n (%)	445 (29.9)	203 (28.9)	141 (29.7)	101 (32.5)	<0.001
Female, n (%)	566 (38.0)	278 (39.5)	175 (36.9)	113 (36.3)	0.519
Country of birth, n (%)					<0.001
Australia	642 (43.1)	335 (47.7)	220 (46.4)	87 (28.0)	
Asia	67 (4.5)	25 (3.6)	22 (4.6)	20 (6.4)	
Europe	607 (40.8)	240 (34.1)	189 (39.9)	178 (57.2)	
Other	172 (11.6)	103 (14.7)	43 (9.1)	26 (8.4)	
Interpreter required, n (%)	170 (11.4)	54 (7.7)	60 (12.7)	56 (18.0)	<0.001
Patient from aged care residential facility, n (%)	36 (2.4)	12 (1.7)	12 (2.5)	12 (3.9)	<0.001
Married or in a de facto relationship, n (%)	762 (51.2)	363 (51.6)	236 (49.8)	163 (52.4)	0.433
Type of NSTE-ACS, n (%)					0.032
Unstable angina	341 (22.9)	177 (25.2)	109 (23.0)	256 (82.3)	
NSTEMI	1,147 (77.1)	526 (74.8)	365 (77.0)	55 (17.7)	
Comorbidities, n (%)					
Atrial fibrillation	393 (26.4)	174 (24.8)	120 (25.3)	99 (31.8)	0.050
Congestive heart failure	378 (25.4)	133 (18.9)	111 (23.4)	134 (43.1)	<0.001
Peripheral vascular disease	32 (2.2)	8 (1.1)	15 (3.2)	9 (2.9)	0.038
Cerebrovascular disease	58 (3.9)	29 (4.1)	17 (3.6)	12 (3.9)	0.895
Paraplegia	28 (1.9)	11 (1.6)	9 (1.9)	8 (2.6)	0.552
Smoking (current), n (%)	46 (3.1)	25 (3.6)	16 (3.4)	5 (1.6)	0.232
Admitted to ICU, n (%)	307 (20.6)	149 (21.2)	100 (21.1)	58 (18.6)	0.623
Developed complication, n (%)					
Any	845 (56.8)	373 (53.1)	283 (59.7)	189 (60.8)	0.022
Pneumonia	138 (9.3)	49 (7.0)	47 (9.9)	42 (13.5)	0.004
Sepsis	64 (4.3)	22 (3.1)	21 (4.4)	21 (6.8)	0.034
UTI	35 (2.4)	16 (2.3)	12 (2.5)	7 (2.3)	0.941
Coronary interventional procedures, n (%)					
PCI	364 (24.5)	217 (30.9)	110 (23.2)	37 (11.9)	<0.001
CABG	190 (12.8)	111 (15.8)	56 (11.8)	23 (7.4)	0.001

Table 1 (*continued*)

Table 1 (*continued*)

Variables	All (n=1,488)	Number of non-cardiovascular comorbidities*			P value†
		0 (n=703)	1 (n=474)	≥2 (n=311)	
IRSAD, n (%)					<0.001
Quintile 1 (most disadvantaged)	296 (19.9)	158 (22.5)	95 (20.0)	43 (13.8)	
Quintile 2	297 (20.0)	153 (21.8)	98 (20.7)	46 (14.8)	
Quintile 3	295 (19.8)	112 (15.9)	101 (21.3)	82 (26.4)	
Quintile 4	320 (21.5)	136 (19.3)	94 (19.8)	90 (28.9)	
Quintile 5 (least disadvantaged)	280 (18.8)	144 (20.5)	86 (18.1)	50 (16.1)	
Admission year, n (%)					0.511
2013	331 (22.2)	151 (21.5)	108 (22.8)	72 (23.2)	
2014	532 (35.8)	240 (34.1)	179 (37.8)	113 (36.3)	
2015	625 (42.0)	312 (44.4)	187 (39.5)	126 (40.5)	

*, from a possible 13; †, differences between proportions were assessed via chi square test and means by one-way ANOVA. n, number of patients; SD, standard deviation; CCI, Charlson comorbidity index; ICU, intensive care unit; IRSAD, Index of Relative Socio-economic Advantage and Disadvantage; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; UTI, urinary tract infection.

had two or more. *Table 1* summarizes the sociodemographic and clinical characteristics of the NSTE-ACS according to their number of NCCs. No gender differences among the various groups of patients were observed, but patients without NCCs were younger than those with NCCs. Patients with NCCs were more likely to be born overseas than in Australia. The occurrence of AF, chronic heart failure and peripheral vascular disease were less frequent among patients without NCCs.

Prevalence of NCCs

The prevalence of diabetes, renal disease, CPD, anemia, cancer and dementia among the NSTE-ACS patients were 29.8%, 23.3%, 10.0%, 6.3%, 4.6% and 3.0%, respectively. The prevalence of the remaining NCCs were each less than 2%. We observed 38 unique NCC dyads. The five most prevalent NCC dyads were diabetes + renal disease (12.9%), CPD + renal disease (2.9%), diabetes + anemia (2.8%), anemia + renal disease (2.7%) and diabetes + CPD (2.4%). The expected prevalence of the top five NCC dyads were diabetes + renal disease (6.9%), CPD + renal disease (2.3%), diabetes + anemia (1.9%), anemia + renal disease (1.5%) and diabetes + pulmonary disease (2.9%). The differences in expected (E) and observed (O) prevalence of NCC dyads were significant only for diabetes + renal disease and anemia + renal disease (i.e., O/E>1, P value <0.05). For the remaining top 5 NCC dyads, no differences in the expected and observed prevalence were observed.

LOS

The median LOS of the cohort was 4.31 days [interquartile range (IQR) 2.17 to 8.92 days]. The unadjusted median LOS among patients with UA was 2.88 days (IQR 1.13–6.92) compared to 5.04 days (IQR 2.67–9.68) for patients with NSTEMI (P value for difference <0.001). The unadjusted median LOS for individual NCCs and their groupings are presented in *Table 2*. Having renal disease [incidence rate ratio (IRR) 1.10; 95% CI: 1.01–1.19; P=0.023] or CPD (IRR 1.13; 95% CI: 1.02–1.25; P=0.027) was associated with increased likelihood of longer LOS than not having these comorbidities. The unadjusted median LOS among patients with 0, 1 and ≥2 NCCs were 3.83 days (IQR 1.96–8.04), 4.40 days (IQR 2.38–8.92) and 5.83 days (IQR 3.04–10.5) (P value for difference <0.001), respectively. Compared to being without NCCs, having one NCC was not associated with greater likelihood of increased LOS (IRR 1.07; 95% CI: 0.99–1.15; P=0.085). However, having two or more NCCs was associated with a 22% increased likelihood of longer LOS compared to not having any NCCs (IRR 1.22; 95% CI: 1.11–1.33; P<0.001).

Table 2 Occurrence and association of non-cardiovascular comorbid conditions with hospital length of stay

Variables	No. of patients	Median LOS (IQR)	IRR (95% CI)	P value
Individual NCCs[a]				
Chronic pulmonary disease	148	5.44 (2.96–8.83)	1.13 (1.02–1.25)	0.027
Diabetes	444	4.96 (2.46–9.83)	1.04 (0.96–1.12)	0.266
Anaemia	93	5.04 (3.12–9.70)	1.09 (0.96–1.25)	0.176
Dementia	44	3.98 (1.56–9.56)	1.08 (0.90–1.30)	0.421
Cancer	69	5.46 (2.71–10.04)	1.07 (0.92–1.24)	0.408
Renal disease	347	5.92 (3.17–10.75)	1.10 (1.01–1.19)	0.023
NCC dyad[b]				
Diabetes and renal disease cluster				
No diabetes + no renal disease	889	4.00 (2.04–8.46)	1.0	–
Diabetes + no renal disease	252	4.08 (1.94–8.25)	1.00 (0.92–1.09)	0.989
No diabetes + renal disease	155	5.45 (3.17–10.63)	1.05 (0.94–1.17)	0.375
Diabetes + renal disease	192	5.98 (3.15–10.81)	1.19 (1.07–1.31)	0.001
Anaemia and diabetes cluster				
No diabetes + no anaemia	992	4.08 (2.13–8.79)	1.0	–
Diabetes + no anaemia	403	4.95 (2.29–9.46)	1.05 (0.97–1.13)	0.231
No diabetes + anaemia	52	4.96 (2.90–8.44)	1.14 (0.96–1.35)	0.137
Diabetes + anaemia	41	5.08 (3.29–11.79)	1.11 (0.91–1.34)	0.300
Renal disease and anaemia cluster				
No anaemia + no renal disease	1,088	4.00 (1.96–8.46)	1.0	–
Renal disease + no anaemia	307	5.92 (3.17–10.75)	1.11 (1.02–1.21)	0.010
No renal disease + anaemia	53	5.04 (3.13–8.46)	1.14 (0.97–1.35)	0.106
Renal disease + anaemia	40	4.96 (3.15–11.15)	1.15 (0.95–1.39)	0.152
CPD and diabetes cluster				
No CPD + no diabetes	931	4.08 (2.08–8.79)	1.0	–
CPD + no diabetes	113	5.38 (3.04–8.71)	1.15 (1.02–1.29)	0.025
No CPD + diabetes	409	4.96 (2.38–9.83)	1.04 (0.97–1.13)	0.271
CPD + diabetes	35	5.46 (2.88–9.71)	1.12 (0.91–1.38)	0.272
Renal disease and CPD cluster				
No CPD + no renal disease	1,036	3.98 (1.96–8.29)	1.0	–
CPD + no renal disease	105	5.00 (2.67–8.67)	1.10 (0.97–1.25)	0.128
No CPD + renal disease	304	5.89 (1.79–10.75)	1.09 (1.01–1.19)	0.041
CPD + renal disease	43	5.92 (3.50–10.75)	1.34 (1.11–1.61)	0.002
Total number of NCCs[†]				
0	703	3.83 (1.96–8.04)	1.0	–
1	474	4.40 (2.38–8.92)	1.07 (0.99–1.15)	0.085
≥2	311	5.83 (3.04–10.5)	1.22 (1.11–1.33)	<0.001

[†], from a possible 13; [a], only non-cardiovascular comorbid conditions with prevalence >2% are presented; [b], only the top 5 most prevalent non-cardiovascular comorbid dyads are presented. IQR, interquartile range; IRR, incidence rate ratio; CPD, chronic pulmonary disease; NCC, non-cardiovascular comorbidity.

Patients with diabetes but no renal disease (IRR 1.00; 95% CI: 0.92–1.09; P=0.989) and patients with renal disease but no diabetes (IRR 1.05; 95% CI: 0.94–1.17; P=0.375) were no more likely to experience a longer LOS than patients without diabetes or renal disease. Conversely, patients with both diabetes and renal disease experienced a 19% (IRR 1.19; 95% CI: 1.07–1.31; P=0.001) greater likelihood of increased LOS compared to patients without diabetes or renal disease. Similarly, in comparison to patients with neither CPD nor renal disease, those with CPD but no renal disease did not experience a significant increase in the likelihood of longer LOS (IRR 1.10; 95% CI: 0.97–1.25; P=0.128). On the other hand, the co-existence of CPD and renal disease was associated with a 34% increased likelihood of longer LOS (IRR 1.34; 95% CI: 1.11–1.61; P=0.002).

In-hospital mortality

Overall, in-hospital death occurred in 6.1% of the cohort, 2.6% in patients with UA and 7.1% among patients with NSTEMI (P value for difference =0.003). The unadjusted mortality rates for individual NCCs and their groupings are presented in *Table 3*. Having cancer was associated with over two times greater likelihood of in-hospital death compared to not having cancer [hazard ratio (HR), 2.06; 95% CI: 1.04–4.07; P=0.038]. Similarly, NSTE-ACS patients with renal disease were about 71% more likely to die compared to those without renal disease (HR, 1.71; 95% CI: 1.03–2.82; P=0.037). The unadjusted in-hospital mortality rate among patients with 0, 1 and ≥2 NCCs were 4.4%, 5.5% and 10.6%, respectively (P value for difference =0.001). *Figure 1* depicts the Kaplan-Meier survival curves of the NSTE-ACS patients according to their total number of NCCs. The presence of single NCC was not associated with a significant increase in the likelihood of in-hospital death (HR, 1.11; 95% CI: 0.65–1.90; P=0.707), whereas having two or more was associated with 79% increased likelihood of in-hospital death (HR, 1.79; 95% CI: 1.06–3.03; P=0.029), compared to not having any NCC. Compared to patients without diabetes or renal disease, those with both diabetes and renal disease were more than twice as likely to die in hospital (HR 2.16, 1.21–3.85; P=0.009). Patients with CPD but no diabetes were no more likely to die than patients with neither (HR, 1.01; 95% CI: 0.58–1.76; P=0.963). However, their co-existence was associated with an increased risk of death (HR, 2.60; 95% CI: 1.06–6.39; P=0.036).

Discussion

In this large short-term study, there was a high burden of NCCs among older adults hospitalized for NSTE-ACS. Some NCC dyads also occurred more frequently than would have been expected. Overall, patients with a higher burden of NCCs experienced a longer LOS and higher mortality rates during hospitalization. In addition, certain NCC dyads exhibited multiplicative effects such that their impact on patients' LOS or likelihood of in-hospital death exceeded the sum of the individual contributory effects of the component conditions.

In this study population, more than half of the patients had at least one NCC and around one-fifth had two or more. Previous international studies have reported varying prevalence of NCCs among patients with ACS, ranging from 10% among AMI patients in Vietnam (32) to over 60% among AMI patients in the United States (33,34). Regardless, the majority of prior studies have focused on populations which were younger than our study participants, with some also including a mix of STEMI and NSTEMI cases. Among the 13 NCCs examined, diabetes was the most prevalent. Our results are in accord with the findings from other contemporary studies. In the Worcester Heart Attack Study that examined trends in the frequency of multiple comorbidities among patients hospitalised for AMI from 1990 to 2007, diabetes was the most prevalent NCC (33). Taken together with prior research, our results suggest a high burden of NCCs among ACS patients.

Although the occurrence of NCC dyads was expected, the observed prevalence of some dyads exceeded the expected prevalence, suggestive of possible clustering. There are multiple explanations for such a high rate of NCC dyads in our study population. First, due to the link between ageing and the development of chronic diseases, the occurrence of multiple pathologies is prevalent among older adults. A recent systematic review estimated that more than 66% of older adults in ambulatory settings had two or more chronic medical conditions (35). Second, in light of the strong pathophysiological associations between diseases such as diabetes and renal disease, "causal comorbidity" has likely contributed to clustering of these conditions in our elderly patient population. In a recent Mendelian randomisation analysis involving 11,502 participants, the study authors concluded there was evidence for a causal association between type 2 diabetes and chronic kidney disease (36). Moreover, due to reduced production of erythropoietin as a consequence of kidney damage, anemia

Table 3 Occurrence and association of non-cardiovascular comorbid conditions with in-hospital mortality

Variables	No. of patients	Mortality rate (%)	HR (95% CI)	P value
Individual NCCs[a]				
Chronic pulmonary disease	148	11.5	1.62 (0.93–2.84)	0.090
Diabetes	444	6.8	1.15 (0.71–1.88)	0.563
Anaemia	93	5.4	0.37 (0.14–0.98)	0.047
Dementia	44	11.4	1.55 (0.60–3.96)	0.362
Cancer	69	14.5	2.06 (1.04–4.07)	0.038
Renal disease	347	10.1	1.71 (1.03–2.82)	0.037
NCC dyad[b]				
Diabetes and renal disease cluster				
No diabetes + no renal disease	889	5.1	1.0	–
Diabetes + no renal disease	252	4.0	0.84 (0.41–1.78)	0.652
No diabetes + renal disease	155	9.7	1.35 (0.71–2.58)	0.355
Diabetes + renal disease	192	10.4	2.16 (1.21–3.85)	0.009
Diabetes and anaemia cluster				
No diabetes + no anaemia	992	6.0	1.0	–
Diabetes + no anaemia	403	6.5	1.02 (0.62–1.68)	0.932
No diabetes + anaemia	52	1.9	0.15 (0.02–1.12)	0.064
Diabetes + anaemia	41	9.8	1.28 (0.44–3.69)	0.649
Renal disease and anaemia cluster				
No anaemia + no renal disease	1,088	4.9	1.0	–
Renal disease + no anaemia	307	9.8	1.16 (0.42–3.2)	0.775
No renal disease + anaemia	53	3.8	0.50 (0.12–2.05)	0.333
Renal disease + anaemia	40	12.5	1.48 (0.91–2.41)	0.113
CPD + diabetes				
No CPD + no diabetes	931	5.3	1.0	–
CPD + no diabetes	113	5.9	1.01 (0.58–1.76)	0.963
No CPD + diabetes	409	9.7	1.41 (0.71–2.79)	0.327
CPD + diabetes	35	17.1	2.60 (1.06–6.39)	0.036
Renal disease + CPD cluster				
No CPD + no renal disease	1,036	4.3	1.0	–
CPD + no renal disease	105	9.5	2.13 (1.01–4.47)	0.045
No CPD + renal disease	304	9.2	1.80 (1.05–2.93)	0.033
CPD + renal disease	43	16.3	2.84 (1.13–7.11)	0.025
Total number of NCCs[†]				
0	703	4.4	1.0	–
1	474	5.5	1.11 (0.65–1.90)	0.707
≥2	311	10.6	1.79 (1.06–3.03)	0.029

[†], from a possible 13; [a], only non-cardiovascular comorbid conditions with prevalence >2% are presented; [b], only the top 5 most prevalent non-cardiovascular comorbid dyads are presented. HR, hazard ratio; CI, confidence interval; CPD, chronic pulmonary disease; NCC, non-cardiovascular comorbidity.

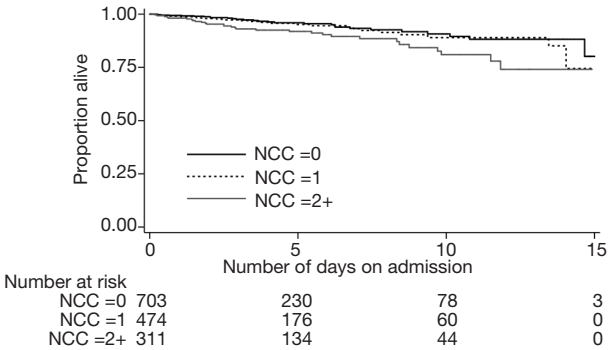

Figure 1 Kaplan Meier survival curves for patients hospitalized for non-ST elevation acute coronary syndrome stratified by their total of non-cardiovascular comorbid conditions.

is often common among patients with renal disease (37), which may explain the higher co-occurrence of renal disease and anemia among our study population.

We found that the occurrence of an additional NCC on top of an existing one may sometimes result in a multiplicative rather than an expected additive effect. For example, while patients with renal disease but no CPD were slightly (9%) more likely to experience longer LOS than those with neither condition, their co-existence was associated with a 34% increased risk of longer LOS. Similarly, whiles patients with diabetes but no renal disease did not experience significantly higher risk of deaths than those with neither condition, their co-existence was associated with over two times increased risk of in-hospital death. The extent to which the addition of another NCC to an existing one increases the biological vulnerability of ACS patients deserves further exploration.

Our observation that the occurrence of multiple NCCs is associated with poor short-term survival and increased hospital LOS may also reflect sub-optimal care for patients with comorbidities, given that the majority of clinical trials and, in turn, practice guidelines, are almost exclusively single-disease focused (11,12). In practice, patients with comorbidities are vulnerable to higher rates of complications from ACS treatment, such as bleeding, owing to factors such as drug–drug interactions and drug-disease interactions (33,38). This may result in complex clinical scenarios for which standard clinical management guidelines may be irrelevant. Thus, our results suggest that further population-based data on the use and impact of contemporary ACS treatments and guidelines in patients with multiple comorbid conditions are needed. Importantly, policy makers or authoritative professional bodies who are responsible for monitoring clinical protocols and for developing ACS guidelines need to acknowledge the existence of significant numbers of patients who are affected by multiple comorbidities. Although, recent European Society of Cardiology (ESC) guidelines for the management of ACS in patients presenting without persistent ST-segment elevation has highlighted the need for greater considerations of comorbidities (39), there remains much room for improvement in the recognition of comorbidities in ACS guidelines. Furthermore, clinicians whose specialty focuses on specific conditions also need to be aware of the high proportion of their patients with multiple chronic conditions in order to know how to coordinate their care with other clinical providers.

A number of limitations to our study warrant mention. First, our analysis was based on hospital administrative hospital data that were not collected for research purposes. Some studies have found that administrative data may lack completeness and at times under-estimate comorbidities (40). Nonetheless, the quality of administrative data has improved significantly in recent times, resulting in their increased use for research purposes (41). Moreover, a recent study found good agreement between medical records and claims (administrative) data when evaluating the presence of comorbidities such as HIV, renal disease, dementia, cancers, cerebrovascular disease and liver disease (42). Furthermore, despite the limitations of administrative data, they outperform snapshot chart reviews for comorbidity assessment (43). Methodologically, we also utilized all available patient records (outpatient attendance, emergency services and all hospitalisations records) prior to admission for the ACS which increased the likelihood of any comorbidities being documented/identified. However, information was not available in the administrative dataset for important covariates such as disease severity, laboratory and imaging results and drug treatments (44). Second, some of our sub-group analyses may have been underpowered and a larger-sample based study may be needed to further explore the direction of impact. Third, our sample population was selected from a single hospital, therefore, selection bias may limit the generalisability of our findings. Fourth, not all NCCs have been examined in this study and as such future studies could examine the prognostic impact of other NCCs not examined in this study. Lastly, the use of only in-hospital data meant that we could not examine the impact of NCCs on longer-term post-discharge outcomes among the ACS patients.

Conclusions

Among older patients hospitalized with NSTE-ACS, there is a high burden of NCCs. Some NCC dyads also occurred more frequently than expected suggestive of a possible clustering. In general, a higher burden of NCCs correlated with increased LOS and poorer survival. These findings highlight the need for contemporary ACS clinical treatment guidelines to recognise and incorporate protocols for the treatment of individuals with multiple chronic conditions to reduce the occurrence of adverse outcomes.

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Footnote

Conflicts of Interest: S Zoungas reports past participation in advisory boards/educational meetings/research on behalf of Monash University (for work unrelated to this paper) with AstraZeneca Pty Ltd., Eli Lilly Australia Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd and Novo Nordisk Pty Ltd. D Liew reports past participation in advisory boards and/or receiving honoraria from Abbvie, Astellas, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi and Shire for work unrelated to this study. The other authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Alfred Hospital Human Research Ethics Committee (project Number 146/17).

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Supplementary

Table S1 Categories and their ICD-10 AM codes*

Category	ICD 10 AM codes recorded
Hypertension	I10
Smoking (current)	Z720, FI17
Congestive heart failure	I50
Obesity	E66, E660, E661, E662, E668, E669
Renal disease	N01, N03, N18, N19, N25 N052, N053, N054, N055, N056, N072, N073, N074
Connective tissue disorder	M32, M34, M332, M069, M060, M059, M058, M053, M050, M051, M353, M063, M052
Cancer	C0, C1, C2, C3, C5, C6, C40, C41, C43, C45, C46, C47, C48, C49, C70, C71, C72, C73, C74, C75, C76, C887, C889, C900, C81, C82, C83, C84, C85, C883, C77, C78, C79, C80, C81, C82, C83, C84, C85, C883, C91, C92, C93, C95, C96, C901, C940, C941, C942, C943, C9451
Diabetes	E104, E114, E134, E144, E102, E112, E132 E142, E103, E113, E133, E143 E109, E119, E139, E149, E105, E115 E135, E145, E101, E111, E131, E141
Peptic ulcer disease	K25, K26, K27, K28
Depression	F32, F33, F204, F313, F314, F315, F341, F412, F432
Pulmonary disease	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67
Anaemia	D51, D52, D53, D508, D509, D500
Dementia	F00, F01, F02, F051
Psychoses	F20, F22, F23, F24, F25, F28, F29, F302, F312, F315
Peripheral vascular disease	I71, R02, I790, I739, Z958, Z959
HIV/AIDS	B20, B21, B22, B23, B24
Cerebrovascular disorders	I60 , I61, I62, I63, I64, I65, I66, G46, I69 I670, I678, I671, I672, I674, I675, I676, I677 I679, G450, G451, G452, G458, G459 I681, I682, G454, I688
Atrial fibrillation	I48

*, The International Classification of Diseases, Revision 10, Australian Modification codes are specified as 3, 4 or 5-digits. If 3-digits are listed then each of the last 2 digits can be from 0 to 9, depending on the specific codes.