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Long-term cohort study of patients presenting with hypercapnic respiratory failure

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ABSTRACT

Objective We sought to describe the long-term prognosis for a population-based cohort of people with hypercapnic respiratory failure (HRF) and the associations between underlying diagnoses and the risks of death and rehospitalisation.

Methods We performed a historical cohort study of all persons with HRF in the Liverpool local government area in New South Wales, Australia, in the 3-year period from 2013 to 2015. Cohort members were identified using arterial blood gas results from Liverpool Hospital demonstrating pH ≤7.45 and $PaCO_2$ >45 mm Hg within 24 hours of presentation. Linked health data were obtained from statewide registries with a minimum follow-up period of 6 years. The primary outcomes were time to death from any cause and the standardised mortality ratio (SMR) which compares the observed to the expected number of deaths in the same population. Secondary outcomes were time to rehospitalisation and the associations between death and/or hospitalisation and underlying diagnoses.

Results The cohort comprised 590 adults aged between 15 and 101 years. Overall, 415 (70.3%) participants died in the follow-up period. Among those who survived the index admission, the probability of survival at 1, 3 and 5 years was 81%, 59% and 45%, respectively. The overall SMR was 9.2 (95% CI 7.6 to 11.0), indicating a near 10-fold risk of death than otherwise expected for age. Most (91%) survivors experienced rehospitalisation, with median (IQR) time to readmission of 3.9 (1.2–10.6) months. Congestive cardiac failure and neuromuscular disease were associated with an increased risk of death, whereas chronic obstructive pulmonary disease and sleep disordered breathing increased the risk of rehospitalisation.

Conclusions HRF is associated with poor survival and high risk of rehospitalisation in the 5 years following an index event. The underlying disease appears to have some influence on overall survival and subsequent hospitalisations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is limited long-term data on clinical outcomes of people with hypercapnic respiratory failure (HRF) irrespective of the underlying cause, and no studies have compared outcomes with those of the reference or source population.

WHAT THIS STUDY ADDS

⇒ An episode of HRF portends an abbreviated survival time with 1-year, 3-year and 5-year survival probabilities of 81%, 59% and 45%, respectively, and the standardised mortality ratio of 9.2 indicates a near 10-fold risk of death compared with an unaffected population of similar age.

⇒ Among the survivors, there is a high risk of rehospitalisation, with 91% being readmitted after a median time of 3.9 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides important epidemiological data fundamental to health planning and service provision, and for interpreting and evaluating the impact of population-based interventions.

INTRODUCTION

Most of the available epidemiological data on hypercapnic respiratory failure (HRF) relate to its association with specific underlying causes, such as chronic obstructive pulmonary disease (COPD).[1 2] However, there are few data on the prevalence and prognosis of HRF as a single entity. This is an important gap in knowledge because systematic evaluation of patients with HRF frequently demonstrates the co-occurrence of multiple diseases with the potential to cause ventilatory failure. For instance, Adler and colleagues found that over half of patients who survived a hospitalisation requiring ventilatory support had at least three major comorbidities known to precipitate acute HRF. Furthermore, in a substantial proportion of this cohort, many of these underlying causes had neither been diagnosed nor treated during the acute admission.[3] Consequently, prognostic information based on prior research studies of persons with specific diagnoses may have limited generalisability to encounters with patients who have undifferentiated HRF and/or multimorbidity.

The few available studies on HRF due to any cause typically recruit participants based on arterial blood gas (ABG) measurements

taken at the time of admission to an intensive care unit, representing a highly selected cohort. Another limitation of the currently available literature is that most studies of prognosis are limited to a relatively short follow-up period. Despite the difficulties associated with defining and identifying a validly representative population-based cohort of patients with HRF, understanding the long-term outcomes of patients with this condition is needed to assist clinical decision-making for individual patients and to determine the effect of interventions directed at prevention and management.

In this study, we sought to determine the prognosis for survival and for rehospitalisation among adults presenting to hospital with HRF due to any cause. We also examined the associations between underlying diagnoses and the risks of death and rehospitalisation, hypothesising that the prognosis in patients with HRF is substantially related to the underlying cause of the condition.

METHODS

We performed a population-based historical cohort study using linked health data. Patients and the public were not directly involved in the production of this study.

Study setting

The cohort comprised adult residents of the Liverpool local government area (LGA), a municipality in Sydney, New South Wales (NSW), Australia, who attended hospital with HRF in the 3-year period from 2013 to 2015. Potential cases were identified by screening ABG records collected at Liverpool Hospital, the major service provider for this region. Liverpool Hospital comprises approximately 900 beds (including dedicated intensive care beds) and provides a range of specialist respiratory and sleep services including provision of non-invasive ward-based ventilation for patients with acute respiratory failure and outpatient services for patients requiring long-term non-invasive ventilatory support therapy.

We considered the participants identified using the above method a representative population cohort based on the following: most patients with HRF are likely to attend hospital in a country with universal (free) healthcare, local data from the Ministry of Health showed that 86% of people from the Liverpool LGA who attended a hospital for respiratory conditions presented to Liverpool Hospital,[4] and patients presenting to our emergency department with respiratory symptoms typically have a venous blood gas performed that prompts a confirmatory arterial sample if HRF is suspected.

Study participants

Inclusion criteria were pH ≤7.45 and $PaCO_2$ >45 mm Hg on the first ABG collected within 24 hours of presentation. We excluded blood gas results in which the SaO_2 was at least 10% lower than the pulse oximetry SpO_2, as these were assumed to be venous specimens. We reviewed medical records to exclude patients who had suffered an out-of-hospital cardiac arrest or in whom the HRF may have been caused by in-hospital procedures requiring general anaesthesia and/or sedation. Further details on this method have been published elsewhere.[5] In defining this cohort, we chose not to differentiate between acute, acute-on-chronic and chronic HRF because the available data did not allow this distinction to be confidently identified and, furthermore, our objective was to assess the prognosis of all patients with HRF, regardless of the time course.

Endpoints

The primary outcome was the time to death from any cause, measured from the date of initial presentation with HRF to the date of death, if this occurred during the follow-up period. In addition to crude death rate, we also estimated the standardised mortality ratio (SMR), defined as the ratio of the observed number of deaths to the expected number of deaths, for the observed age distribution. Secondary outcomes included time to rehospitalisation and the associations between these outcomes and underlying diagnoses.

Follow-up period

The minimum follow-up period for the primary outcome was 6 years. Participants were followed up from the date of initial presentation with HRF (between 1 January 2013 and 31 December 2015) and either the date of death or 31 December 2021, whichever occurred first. Hospital data were available to 30 June 2021, allowing a minimum follow-up period of 5.5 years for the secondary endpoint of rehospitalisation.

Data sources

Data on deaths and hospitalisation were obtained from the following datasets: the NSW Registry of Birth, Deaths and Marriages (RBDM), the NSW Admitted Patient Data Collection (APDC), the NSW Emergency Department Data Collection (EDDC). All deaths occurring in the state of NSW are recorded in the RBDM. The APDC and EDDC contain data on all attendances at NSW public and private hospitals. Members of the study cohort were linked to the deaths and hospitalisation data using probabilistic data linkage. This was performed securely by the Centre for Health Record Linkage (CHeReL) using the following identifiers: name, date of birth, sex, hospital record number, admission date and home address. CHeReL were not otherwise involved in this study and provided the investigators with an anonymised linked dataset.

Data collection

We obtained demographic and clinical information on members of the study cohort from the APDC. These data included the presence of specific diagnoses recorded at

any admission and coded using the International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM).[6] Diagnoses were extracted from all available hospital admissions data, including those up to 5 years before the index admission, during the index admission and during the period of follow-up after the initial presentation with HRF. Specific diagnoses or potential causes, of interest, because of their relation to HRF, were chronic obstructive pulmonary disease (COPD), congestive cardiac failure (CCF), sleep disordered breathing (SDB), neuromuscular disease (NMD) and opioid use that were reliably recorded in the medical record. We identified a range of ICD-10-AM codes corresponding to each of these potential causes and then used these codes for data extraction. Some other factors of potential interest, such as smoking status, obesity status or body mass index were not routinely recorded in the medical record and, hence, could not be used. Details of each of the ICD-10-AM codes used are provided in the online supplemental table S1. The overall degree of comorbidity was quantified using the Charlson Comorbidity Index (CCI), which has been shown to be an independent predictor of mortality.[7]

Data analysis

Data were summarised using frequencies with percentages for categorical variables and either means with SD or medians with IQRs for continuous variables depending on the distribution of values. Stratified Kaplan-Meier survival curves were generated for the primary outcome, death from any cause. Age-standardised death rates were calculated using person-years of follow-up. The SMR was calculated based on expected mortality in the NSW population stratified by age.[8] We used Cox proportional hazards regression models to determine the associations between underlying causes and the risks of death and rehospitalisation. Covariates that were included in these models were selected to reflect explicit assumptions about causal pathways. These were encoded in a directed acyclic graph (DAG), as shown in the online supplemental figure S1.[9] The final multivariate model, based on these assumptions, included the following covariates: age, socioeconomic status (financial status on admission, marital status, country of birth) and the degree of hypercapnia ($PaCO_2$). DAGs were constructed and minimum sets of adjustment covariates were identified using the web-based program 'dagitty'.[10] All analyses were performed in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The cohort comprised 590 adults aged between 15 and 101 years. Acidosis (pH <7.35) was present in 320 (54%) adults at initial presentation. All were admitted via the emergency department. Participant characteristics are shown in table 1.

Table 1 Cohort characteristics

N	590
Age, mean (SD)	68.5 (16.3) years
Sex, male (%)	297 (50.3%)
Country of birth, n (%)	
Australia	265 (45%)
Other	324 (55%)
Not recorded	1 (<0.01%)
Arterial blood gas values, median (IQR)	
pH	7.34 (7.28–7.38)
pCO_2	53 (48–61)
pO_2	76 (60–113)
Bicarbonate	29 (26–32)
Potential underlying cause for hypercapnia, n (%)	
Chronic obstructive pulmonary disease	353 (60%)
Congestive cardiac failure	289 (49%)
Sleep disordered breathing	121 (21%)
Opioid use	108 (18%)
Neuromuscular disease	15 (2.5%)
Charlson Comorbidity Index, median (IQR)	7 (4–9)

Mean follow-up time for the primary outcome was 7.5 years. At least one of the prespecified causes of HRF was recorded in 84%, at least two causes in 47% and at least three causes in 17% of study participants. The distribution and degree of overlap between various prespecified causes is shown in figure 1.

Deaths

Overall, 415 (70.3%) participants died during the follow-up period. Seventy-seven (13%) died during the index admission. Among those who survived the index admission, the probability of survival at 1, 3 and 5 years was 81%, 59% and 45%, respectively. There was a significant variation across age groups, as shown in figure 2. Median (IQR) survival was 5.2 (3.5, 7.4) years among those aged 60–69 years, 3.4 (2.6, 4.4) years among those aged 70–79 years, and 1.9 (1.4, 2.6) years among those aged 80 years or more. Both pH and severity of hypercapnia at presentation had a significant impact on subsequent survival (p<0.001); stratified survival curves are shown in figure 3.

The overall death rate was 144 (95% CI 117 to 171) deaths per 1000 person-years at risk with SMR being 9.2 (95% CI 7.6 to 11.0), indicating that people admitted with HRF have substantially higher mortality than otherwise expected for their age. Age-stratified death rates are provided in the online supplemental table S2.

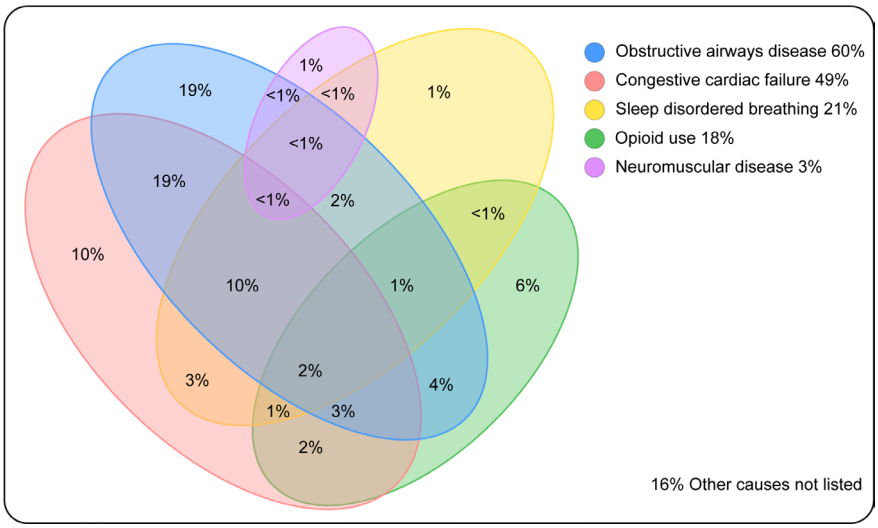

Figure 1 Prevalence of potential causes for hypercapnic respiratory failure, alone and in combination, within the study cohort. At least one prespecified cause was recorded in 84%, at least two causes in 47% and three causes in 17% of the cohort. This is a non-proportional (not-to-scale) Venn diagram.

Rehospitalisations

Of the 513 participants who survived the index presentation with HRF, 469 (91%) experienced rehospitalisation during the study period. Median (IQR) time to rehospitalisation was 3.9 (1.2–10.6) months. The HR for rehospitalisation was significantly associated with increasing age (p=0.003) but not the degree of hypercapnia (p=0.8) nor the presence of acidosis (p=0.2).

Effect of underlying cause

The frequency of underlying potential causes among survivors of the index admission and their associations with the risks of death and rehospitalisation are shown in table 2. The presence of a diagnosis of CCF was associated with an adjusted HR of 1.62 (95% CI 1.30, 2.01) for death and 1.34 (95% CI 1.10, 1.64) for rehospitalisation, compared with those without CCF. Recorded diagnoses of COPD and SDB were not associated with a significantly increased risk of death but were associated with increased of rehospitalisation. Patients in whom opioid use was recorded as a diagnosis had a lower risk of death compared with the rest of the cohort, with an adjusted HR of 0.74 (95% CI 0.55, 0.99). Among the prespecified causes, NMD had the highest adjusted HR for death at 2.38 (95% CI 1.16, 4.90).

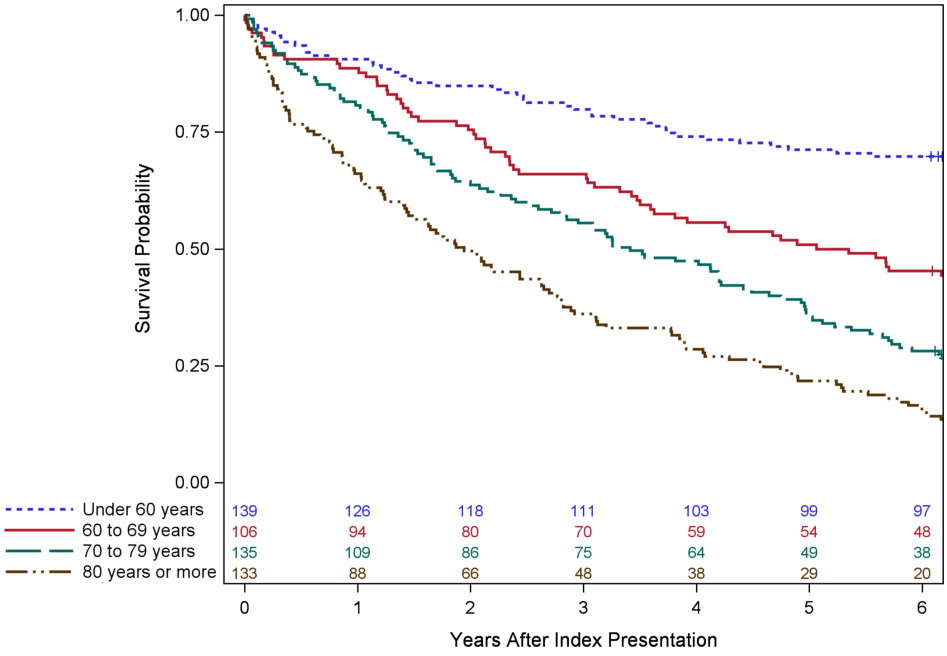

Figure 2 Survival estimates by age strata following discharge from hospital with hypercapnic respiratory failure. Numbers in coloured font indicate the number of subjects at risk years after presentation.

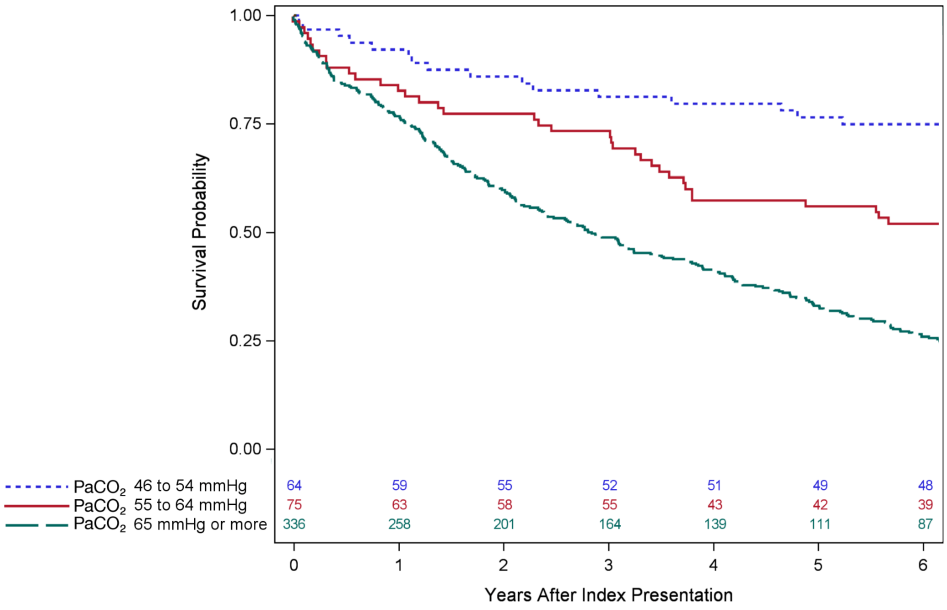

Figure 3 Survival estimates stratified by admission $PaCO_2$ among survivors of the index presentation with hypercapnic respiratory failure. Numbers in coloured font indicate the number of subjects at risk years after presentation.

DISCUSSION

This is the first population-based longitudinal study of people with hypercapnia, and the first cohort study to describe prognosis beyond 5 years. We found that hospitalisation with HRF heralds a high risk of rehospitalisation and death in subsequent years, particularly among older people. Most people had at least one identifiable underlying cause and many had two or more potential causes occurring concurrently. After adjustment for age and other potential confounders, people diagnosed with NMD and CCF had the worst prognosis for survival, and people with opioid use as the potential cause for HRF had the best prognosis. Our findings underscore the importance of HRF and confirm the importance of addressing underlying diagnoses to improve clinical outcomes associated with this condition.

The overall 5-year survival probability of under 50% illustrates the substantial mortality imposed by HRF. There are limited data on the outcomes of patients with HRF, and there is considerable heterogeneity among existing studies. A recent study found that 44.2% of patients with hypercapnia but not acidosis died within a 2.5-year period.[11] Compared with our study, these subjects were younger and had less comorbidity based on the CCI but had more severe HRF (based on higher $PaCO_2$ values). Another study found that 30% of patients with a documented history of HRF died over 19–31 months of follow-up.[12] However, potential participants with limited life expectancy were excluded from the analysis. Other studies have been limited to 1 year of follow-up,[13 14] restricted to patients requiring non-invasive ventilation (NIV)[15] or based on groups with specific diagnoses such as COPD.[2 16 17] Our study underscores the severe impact of a diagnosis of HRF on life expectancy, regardless of the underlying cause, and provides prognostic evidence to inform clinical decision-making.

In addition to the high rate of death, we found HRF to be associated with a substantially high risk of rehospitalisation. The median readmission time of under 4 months shows the ongoing health impacts for those who survive the index admission. A previous study of patients with HRF found 30-day readmission rates of 23%,[12] comparable to our dataset in which the 25th percentile for time to readmission was 1.2 months. This information is important to health service planners as better understanding of healthcare utilisation is critical to the development of evidence-based enhancements which have been proven to reduce readmission, including positive airway pressure therapy for COPD[18] and SDB.[19]

A range of potential causes for HRF were identified among study participants, and we found that, within the limitations posed by the retrospective method of data collection and reliance on clinical diagnosis codes, these causes had effects on the risk of death and rehospitalisation. The increased risks of death observed with CCF and NMD, relative to other causes, likely reflect the severity of the underlying disease once hypercapnia becomes apparent. Although COPD and SDB did not affect mortality risk, these along with CCF and opioid use increased the risk of rehospitalisation in this cohort. There are inconsistent data on the role of underlying causes with respect to healthcare use; one study of patients with undifferentiated HRF found that hospitalisation in the preceding year was a significant predictor for readmission but the underlying cause was not.[14] Another found peripheral vascular disease but not COPD or CCF increased the 30-day readmission rate.[12] Our results emphasise the need to systematically evaluate and

Table 2 Risk of death and rehospitalisation among survivors of the initial HRF episode, by presence or absence of potential cause (N=513)

Cause	n (%)	Risk of death				Risk of rehospitalisation				Risk of death or rehospitalisation			
		Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
COPD	316 (62%)	1.24 (0.99, 1.56)	0.06	1.11 (0.87, 1.40)	0.4	1.60 (1.32, 1.94)	<0.001	1.58 (1.28, 1.95)	<0.001	1.55 (1.28, 1.88)	<0.001	1.42 (1.15, 1.76)	0.001
CCF	253 (49%)	1.72 (1.38, 2.13)	<0.001	1.62 (1.30, 2.01)	<0.001	1.40 (1.17, 1.68)	<0.001	1.34 (1.10, 1.64)	0.003	1.45 (1.21, 1.74)	<0.001	1.29 (1.05, 1.57)	0.01
SDB	116 (23%)	0.91 (0.71, 1.18)	0.5	0.83 (0.64, 1.09)	0.18	1.37 (1.11, 1.70)	0.004	1.48 (1.19, 1.85)	<0.001	1.36 (1.10, 1.69)	0.005	1.44 (1.15, 1.80)	0.001
Opioid use	101 (20%)	0.68 (0.51, 0.90)	<0.001	0.74 (0.55, 0.99)	0.04	1.35 (1.08, 1.70)	0.008	1.46 (1.16, 1.84)	0.001	1.38 (1.10, 1.73)	0.005	1.63 (1.29, 2.06)	<0.001
NMD	12 (2%)	2.48 (1.32, 4.66)	<0.001	2.38 (1.16, 4.90)	0.02	0.65 (0.34, 1.27)	0.2	0.62 (0.28, 1.36)	0.3	1.18 (0.61, 2.29)	0.62	1.47 (0.64, 3.33)	0.4

*Adjusted for age, financial status on admission, marital status, country of birth and the degree of hypercapnia.
CCF, congestive cardiac failure; COPD, chronic obstructive pulmonary disease; HRF, hypercapnic respiratory failure; NMD, neuromuscular disease; SDB, sleep disordered breathing.

optimally manage conditions such as CCF and COPD, and rationalise opioid use to clinical situations where potential harms are outweighed by the benefits of these medicines.

Our study has several strengths. We have identified a population-based cohort of people with HRF using ABG measurements, thus providing an inclusive picture of this condition. There are several reasons to consider HRF as a single condition for the purpose of epidemiological study. As already mentioned, in many individuals with HRF, multiple underlying causes with the potential to cause hypercapnia may coexist. In clinical practice, these causes may not be immediately apparent, and understanding the risk of death among people with HRF as a group allows for improved prognostication. Furthermore, many people with HRF receive similar treatments, such as domiciliary NIV, suggesting a potential target group for future intervention studies. Few studies have described clinical outcomes associated with a group of people with HRF irrespective of the underlying condition or selected by the type of treatments received,[11 12 14] and none have a follow-up period of more than 3 years. As such, our study provides valuable and novel information regarding this group.

We have used the SMR to demonstrate the increased mortality associated with HRF, a key strength of our study in describing the epidemiological impact of this condition. Although we do not provide information on specific treatments such as ventilation support therapy, the observational nature of our study is such that any attempt to draw inferences based on the outcome of interventions is likely to be influenced by bias and hence obfuscate, rather than clarify, current knowledge based on randomised controlled trials. Rather, by using the SMR, we are able to provide an indicator of the overall survival of this cohort compared with a control or reference population (those without HRF), an index that has never been reported previously in any population.

Our study has also a number of limitations. We did not differentiate between acute and chronic hypercapnia, unlike some previous studies that have done so based on the observed pH.[11 14] As such, the data provided on prognosis and outcomes relate to people with HRF as a whole, with limited generalisability to acute or chronic cases. However, the distinction between acute and chronic states can be challenging, as acute deterioration and a fall in pH can be observed after a seemingly minor insult in patients with chronic HRF. Furthermore, hypoventilation can occur episodically or acutely in patients without diurnal hypercapnia, for example, in association with COPD.[20] In the absence of a consensus case definition for HRF, we adopted an inclusive approach with the goal of estimating the overall prognosis for people with HRF even when the underlying cause or causes are not apparent at initial presentation.

We did not review ABG data prior to the index episode of HRF. Therefore, it is possible that our survival estimates are an underestimate of the true value following

the development of hypercapnia. Nevertheless, the SMR confirms that survival is abbreviated in this cohort. We also acknowledge that some patients with HRF may have been missed if an ABG was not performed within the first 24 hours of presentation. However, a key strength offered by data linkage is the accuracy in outcome measurements, with low likelihood of loss to follow-up, another strength of this study.

Some limitations are related to the historical cohort design of this study. Measurement of exposure variables was based on medical records, specifically whether these diagnoses were recorded in the form of ICD-10-AM codes. This method, while frequently employed in health services research, is a form of repurposing of clinical data for research purposes and is a source of measurement error if these data were not recorded accurately. For instance, the diagnosis of SDB is likely to be underestimated based on administrative data.[21] It is for this reason that we did not include chest wall disorders such as kyphoscoliosis or obesity in our analyses of contributing diagnoses, as we find that typically in clinical practice these conditions are often under-recognised (in case of the former) or poorly recorded (in case of the latter). We also did not differentiate between mild and severe forms of each of these potential causes. However, our approach provides an exploratory analysis of the potential impact of underlying causes on relevant clinical outcomes. Importantly, our results may also challenge perceptions of futility when COPD is found to be a cause of HRF, as this condition was not found to be associated with an increased risk of death when compared with other causes such as CCF.

In conclusion, HRF is associated with poor survival in the 5 years following an index event. For those who survive the initial hospitalisation episode, most are readmitted within a year. The underlying disease appears to have some influence on overall survival and subsequent hospitalisations. Our findings highlight the need for better inventions for long-term management of people with HRF, provide guidance for health service planners in meeting needs for relevant health services and provide a basis for shared decision-making between patients with this condition and clinicians from a range of disciplines.

Contributors Conceptualisation: YC, HV. Methodology: YC, FLG, GBM. Data curation and analysis: YC, FLG. Writing (original draft): YC. Writing, reviewing and editing (final draft): All authors. Supervision: FLG, GBM, HV. Funding acquisition: YC, FLG, HV. HV is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the NSW Population and Health Services Research Ethics Committee (reference HREC/18/CIPHS/20). The NSW Population and Health Services Research Ethics Committee granted a waiver of informed consent in accordance with the National Statement (Section 2.3.10) due to the low risk of the project and the benefits of research outweighing any harms associated with not seeking consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available on reasonable request pending review by the relevant ethics committee.

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Supplementary Material

A long-term cohort study of patients presenting with hypercapnic respiratory failure

Yewon Chung, Frances L. Garden, Guy B. Marks, Hima Vedam.

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Chung Y, *et al. BMJ Open Respir Res* 2024; 11:e002266. doi: 10.1136/bmjresp-2023-002266

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	E66.2	Obesity with alveolar hypoventilation
	E66.20	Obesity with alveolar hypoventilation, body mass index [BMI] not elsewhere classified
	E66.21	Obesity with alveolar hypoventilation, body mass index [BMI] $\geq$ 30 kg/m^2 to $\leq$ 34.99 kg/m^2
	E66.22	Obesity with alveolar hypoventilation, body mass index [BMI] $\geq$ 35 kg/m^2 to $\leq$ 39.99 kg/m^2
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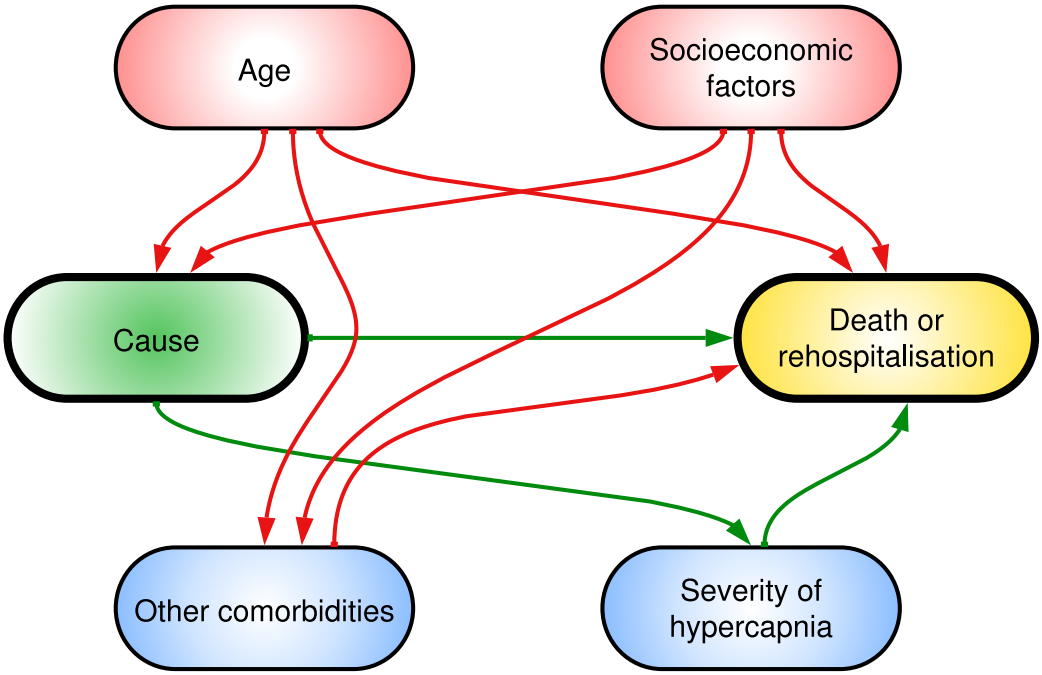

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Supplementary Table S2. *Number of deaths per person-years at risk among adults surviving a hospital admission with hypercapnic respiratory failure for the period 2013 to 2021.*

Age at 2013 (years)	**n (%)**	**Deaths (n)**	**Person-years of follow-up**	**Deaths/1,000 person-years**
15-24	8 (1.6%)	2	50.8	39.4
25-34	20 (3.9%)	4	130.9	30.6
35-44	32 (6.2%)	6	211.5	28.4
45-54	42 (8.2%)	17	243.3	69.9
55-64	75 (14.6%)	40	374.0	107.0
65-74	140 (27.3%)	100	593.2	168.6
75-84	134 (26.1%)	114	454.0	251.1
85-94	60 (11.7%)	53	132.9	398.8
95+	2 (0.4%)	2	3.25	615.4

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	"cohort study"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	"an historical cohort study… linked health data… poor survival and high risk of rehospitalization…"
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	"However, there are few data on the prevalence and prognosis of HRF as a single entity. This is an important gap in knowledge because systematic evaluation of patients with HRF frequently demonstrates the co-occurrence of multiple diseases with the potential to cause ventilatory failure."
Objectives	3	State specific objectives, including any prespecified hypotheses	3,4	"we sought to determine the prognosis for survival and for re-hospitalization… hypothesizing that the prognosis in patients with HRF is substantially related to the underlying cause of the condition"
Methods				
Study design	4	Present key elements of study design early in the paper	4	"population-based historical cohort study using linked health

				data”
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A (not matched)	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7	“Specific diagnoses of interest… were COPD, congestive cardiac failure… sleep disordered breathing… neuromuscular disease… opioid use. “Covariates for these models were determined using a directed acyclic graph (DAG), shown in the online Supplement…”
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7	“Details of the ICD-10-AM codes used for data extraction are provided in the Supplementary Material.”
Bias	9	Describe any efforts to address potential sources of bias	4	“We considered this a representative population cohort based on the following…”

Study size	10	Explain how the study size was arrived at	N/A

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6	"Data were summarised…"
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7	"Age-standardised death rates… "We used Cox proportional hazards regression models… "DAGs were constructed and minimum sets of adjustment covariates identified…"
		(*b*) Describe any methods used to examine subgroups and interactions	N/A	
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	11	"low likelihood of loss to follow-up, another strength of this study"
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A	
		(b) Give reasons for non-participation at each stage		
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Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-13	Table 1, Table 2
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Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7	*"Deaths"* *"Rehospitalizations"*
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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13	Table 2

	(*b*) Report category boundaries when continuous variables were categorized
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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		
Discussion				
Key results	18	Summarise key results with reference to study objectives	9	"The present study shows that hospitalization with HRF heralds a high risk of rehospitalization and death in subsequent years…"
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	"Our study has a number of limitations also…"
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11	"The underlying disease appears to have some influence on overall survival and subsequent hospitalizations…"
Generalisability	21	Discuss the generalisability (external validity) of the study results	10	"We have identified a population-based cohort of people with HRF using arterial blood gas measurements, thus providing an inclusive picture of this condition"
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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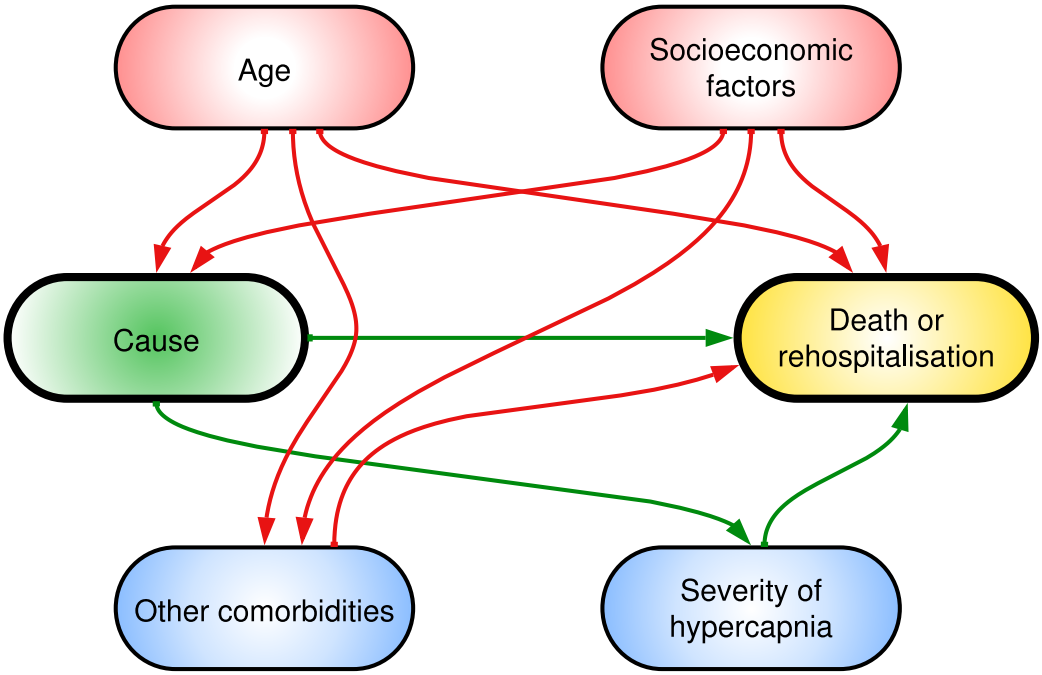

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