The Lancet Regional Health - Europe 5 (2021) 100097

Contents lists available at ScienceDirect

The Lancet Regional Health - Europe

journal homepage: www.elsevier.com/lanepe

Research paper

Underlying conditions and risk of hospitalisation, ICU admission and mortality among those with COVID-19 in Ireland: A national surveillance study

Kathleen E. Bennett[a,b,*], Maeve Mullooly[a,1], Mark O'Loughlin[c], Margaret Fitzgerald[c], Joan O'Donnell[c], Lois O'Connor[c], Ajay Oza[c], John Cuddihy[c]

[a] Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland
[b] Data Science Centre, Royal College of Surgeons in Ireland, Beaux Lane House, Mercer Street Lower, Dublin, Ireland
[c] Health Service Executive, Health Protection Surveillance Centre, Dublin, Ireland

ARTICLE INFO

Article History:
Received 22 January 2021
Revised 8 March 2021
Accepted 23 March 2021
Available online 15 April 2021

Keywords:
COVID-19
Underlying conditions
Mortality
Hospitalisation
ICU admission

ABSTRACT

Background: To date, over 2 million people worldwide have died with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. To describe the experience in Ireland, this study examined associations between underlying conditions and the following outcomes: mortality, admission to hospital or admission to the intensive care unit (ICU) among those infected with COVID-19.

Methods: This study used data from the Health Protection Surveillance Centre in Ireland and included confirmed cases of COVID-19 from the first wave of the pandemic between March and July 2020. Two cohorts were included: all cases (community and hospital) and hospital admissions only. For all cases, health outcome data included mortality and hospitalisation. For hospitalised cases, outcome data included mortality and ICU admission. Logistic regression was used to examine associations between underlying conditions and outcomes across both cohorts. Results are presented as adjusted odds ratios (OR) and 95% confidence intervals (CIs).

Findings: There were 19,789 cases included in analysis, which encompassed 1,476 (7.5%) deaths, 2,811 (14.2%) hospitalisations, and 438 (2.2%) ICU admissions of whom 90 (20.5%) died. Significantly higher risk of mortality, hospitalisation and ICU admission was associated with having chronic heart disease, a BMI $\geq$40kg/m^2 and male sex. Additionally, diagnosis of a chronic neurological condition (OR 1.41; 95%CI:1.17, 1.69), chronic kidney disease (OR 1.74; 95%CI:1.35, 2.24) and cancer (OR 2.77; 95%CI:2.21, 3.47) were significantly associated with higher risk of mortality among all cases, with similar patterns of association observed for mortality among hospitalised cases.

Interpretation: The identification of underlying conditions among COVID-19 cases may help identify those at highest risk of the worst health outcomes and inform preventive strategies to improve outcomes.

Funding: This study was supported by the Health Service Executive, Health Protection Surveillance Centre. KEB and MM are funded by the Health Research Board (RL-15-1579 and EIA-2019-012 respectively).

1. Introduction

Internationally, the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has resulted in approximately 93 million people developing coronavirus disease 2019 (COVID-19) following infection, and over 2 million deaths as of 18th January 2021 [1]. Variations in mortality rates have been observed internationally [1] and although differences are not fully understood, factors that may have contributed include variations in the clinical management of patients with COVID-19 (particularly during the early phase of the pandemic), access to resources, and disparities in healthcare systems. As many countries are now experiencing resurgences in COVID-19 infections, knowledge about the coronavirus disease has increased rapidly, much of which has developed from experiences across different international healthcare settings.

The majority of those who test positive for COVID-19 will survive the disease and the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) states that, based on available data, approximately 80% of those who test positive

* Corresponding author at: Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland.
E-mail addresses: kathleenebennett@rcsi.ie (K.E. Bennett), ajay.oza@hse.ie (A. Oza).
[1] Joint first authors.

https://doi.org/10.1016/j.lanepe.2021.100097

for COVID-19 experience a mild illness or are asymptomatic [2]. In Ireland, the first confirmed case was notified in March 2020 and the most recent data (as of January 18th 2021) shows that there have been over 167,000 confirmed cases [3]. Further, there have now been over 2,300 deaths among confirmed cases [3].

Recent studies have aimed to identify factors associated with adverse COVID-19 outcomes and more studies are presenting health outcome data. Few surveillance studies representative of full populations have been reported, particularly in a European setting. One of those reported was a recent study from Spain [4]. A recent large UK study involving 166 hospitals observed that older age and chronic comorbidities, including obesity, were associated with a higher mortality risk [5]. However most studies have been hospital based or included a local population [5-8]. A recent systematic review and meta-analysis that included fourteen studies, with thirteen from China and one from the United States found that the presence of comorbidities including coronary heart disease, hypertension, or diabetes was associated with significantly higher risk of death among COVID-19 patients [9]. In addition, underlying conditions including cardiovascular disease, obesity, and diabetes have been reported as being associated with higher risk of COVID-19 infection and ICU admission [10].

To further expand this knowledge and to provide a combined community and hospital based perspective, this study aimed to describe the experience in Ireland, using population data from the national Health Protection Surveillance Centre (HPSC) and examine the association of underlying conditions on health outcomes of mortality and hospitalisation in confirmed cases of COVID-19 infection, and mortality and ICU admission in those hospitalised due to COVID-19 in Ireland from 2nd March to 31st July 2020.

2. Methods

2.1. Study overview

This study was reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies [11].

This retrospective cohort study used observational, routinely collected notification surveillance data from confirmed cases of COVID-19 in Ireland. Medical diagnostic laboratories and clinicians in Ireland are required by law to notify cases of COVID-19 to the Department of Public Health (Medical Officer of Health) in the patient's region of residence, who in turn report these cases to the HPSC [12]. Surveillance of COVID-19 in Ireland is thereby conducted by HPSC in conjunction with the eight regional Departments of Public Health and medical diagnostic laboratories. All notification records are housed in the national electronic Computerised Infectious Disease Reporting (CIDR) system and supplementary data on cases of COVID-19 cases are collected from a number of different sources (through Public Health follow-up, the Contact Tracing Management Programme (CMP), enhanced surveillance of cases admitted to intensive care and death registrations) and these data are also collated on CIDR. Defined data is collected on each case and specified in the standardised enhanced surveillance form (ESF).

2.2. Study population and definitions

This study population included those who were confirmed cases of COVID-19 notified to the HPSC in Ireland between 2nd March to 31st July 2020. A confirmed case is defined as any person meeting the laboratory criteria of detection of SARS-CoV-2 nucleic acid in a clinical specimen. The testing policy during the observation period was that cases were tested if they met the following criteria: had symptoms consistent with COVID-19, had travelled to an affected region, were close contacts of a known case or were part of a mass or serial testing programme [13]. Therefore, this study only included cases that were laboratory confirmed. Patients were considered to be hospitalised if they were admitted to hospital for at least one overnight stay (in-patients). Patients were considered as an ICU admission if they were admitted to ICU for any period of time. Governmental guidelines on reporting of COVID-19 deaths were adhered to which followed WHO guidance [14] and a COVID-19 death was defined as a patient who had died after having a confirmed positive test for COVID-19. Where a death occurred, death certificates were used for those who died. Patients were followed up until 14th September 2020, hospital discharge, or death. Analysis of outcomes was conducted separately among two cohorts including (i) the overall study population of all confirmed cases and (ii) hospital admissions only.

2.3. Data collection (exposures and outcomes)

Data were collected using the ESF. Non-severe cases were interviewed via telephone by regional contact tracing centres or regional departments of public health. ESFs on hospitalised patients/severe cases was mainly completed by public health or contact tracing teams, with some information being provided by hospital teams, but this was less common. Teams in each intensive care unit updated on patients in critical care directly. Patient data collected as part of the ESF included age (categorised as 5-year age-bands), sex, community health organisation (CHO), living in a residential care facility (yes/no), and likely source of transmission (close contact of a known confirmed case, community transmission, travel related, healthcare acquired (healthcare acquired (staff) or healthcare acquired (patient)), or unknown/missing). The presence (yes/no) and type of underlying conditions captured included chronic heart disease, chronic neurological condition, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma requiring medication, immunodeficiency condition (including HIV), diabetes, cancer / malignancy, or other condition. Detailed body mass index (BMI) information is not routinely captured by the ESF and instead recorded as the presence or absence of morbid obesity, defined as a BMI of $\geq$40 kg/m^2 (yes / no). Information on the underlying condition of hypertension was not uniformly collected for all cases and was most often recorded in those admitted to ICU. Therefore, it is not included in the analysis to reduce risk of bias in the results. Where an underlying clinical condition was indicated but none of the conditions listed (or pregnancy) were reported, this was classified as 'unknown' for underlying condition. Where an underlying condition was reported as 'pregnant' this was not included as a clinical condition in the analysis (either individually or in the count of multimorbidity).

Outcome measures were examined separately, firstly for all cases and secondly for those requiring hospitalisation. In all cases, outcomes of mortality and hospitalisation were considered. In the hospitalised cases only, the outcomes of admission to ICU and mortality were examined.

2.4. Statistical analysis

Descriptive analysis (frequencies and percentages) of the underlying conditions are presented. Associations between underlying conditions and the three outcomes (hospitalisation, ICU admission, mortality) were examined using logistic regression analysis. Both unadjusted and adjusted analyses are presented as odds ratios (OR) and 95% confidence intervals. A non-linear association between age and each outcome was initially examined using a generalised additive model including a linear and spline term for age (with 4 degrees of freedom). The analysis of deviance gives a X^2 test from comparing the full model and the model with the non-linear term dropped. Where a significant non-linear age association was found for the outcome of interest, age was included as a linear and polynomial (quadratic and/or cubic) term in the logistic regression model. Adjusted

Research in context

Evidence before this study

Prior studies have suggested that specific underlying conditions influence adverse health outcomes among those with a confirmed diagnosis of COVID-19.

Added value of this study

This study provides a population based, nationally representative perspective that captures COVID-19 confirmed cases across all settings in Ireland and shows that patterns of association between COVID-19 and health outcomes are consistent with other international populations.

Implications of all the available evidence

These findings will help inform public health strategies in the management of future public health interventions against COVID-19. This study will help inform the identification of COVID-19 cases that are at highest risk of adverse health outcomes. These findings will also help inform prevention strategies for any potential future resurgence in COVID-19 infections. Further, findings from this study will help identify those who will benefit most from preventive intervention and will inform vaccination decision-making processes at the population level.

logistic regression analysis included all factors identified, age (5-year bands; as linear or higher polynomial), sex, underlying conditions, CHO or area of residence and route of transmission. Where age was modelled as a polynomial the ORs (95%CI) were not included in the tables of results. The overall test of association was examined using the Wald test. Tests of interactions were performed for effect modification between sex, underlying conditions and age (5-year bands).

To address the potential selection bias associated with complete case only analysis, we conducted a sensitivity analysis using inverse probability weighting (IPW) for missing data [15]. IPW assigns more weight to those cases who are more likely to have missing underlying conditions in the dataset but where data on underlying conditions is actually available. The weights are derived from a logistic regression model predicting the likelihood of missing (vs non-missing) of underlying condition, using age (5-year bands), sex, residential care setting and CHO. Trimmed weighting was used by replacing observations with the most extreme weights (1% of all observations) at the lower and upper end of the distribution by the values at 1% and 99% respectively. A naïve variance estimator for calculating 95% confidence intervals was used.

Further, in additional sensitivity analyses, logistic regression was performed replacing the individual underlying conditions with the number of comorbidities (multimorbidity) classified as 0, 1, 2, 3 or ≥4 comorbidities (not including hypertension) for all outcomes included in the main analyses.

Significance at $p<0.05$ was assumed. The analyses were conducted using SAS (v9.4, SAS Institute Inc, Cary, USA).

2.5. Role of the funding source

The funding bodies did not have any role in study design, data collection, data analysis, interpretation and writing of this report.

3. Results

3.1. Analytical population

Initially n=26,106 COVID-19 cases confirmed between 2nd March and 31st July 2020 were identified for inclusion. Confirmed cases were excluded from this analysis where 'any underlying condition' (yes, no, unknown, or missing) was either unknown or missing. Therefore, analyses were restricted to confirmed cases with complete data on underlying conditions. This resulted in a subset of 19,789 (75.8%) confirmed COVID-19 cases included. A higher proportion of women and younger aged cases had missing data on the ESF. Further, regional variation in the proportion of missing data was observed and where data was collected outside residential care settings.

Of the subset with complete data, 14.2% (n=2,811) were hospitalised, 2.2% (n=438) were admitted to ICU, and 7.5% (n=1,476) had died. Among those who had been admitted to ICU, 20.5% (n=90) had died.

3.2. Associations between underlying conditions and mortality among all COVID-19 confirmed cases within the study subset

An overview of associations between the underlying conditions examined in this study and mortality with COVID-19 are shown in Table 1. Men compared to women (OR: 1.66, 95%CI: 1.43, 1.92) were at significantly increased risk of mortality. There was a significant non-linear association between age and mortality (X^2=150.94, $p<0.001$). Compared to those who did not have the underlying condition, there was a statistically significant increased risk of mortality in those with underlying chronic heart disease (OR: 1.28, 95%CI: 1.09, 1.50), chronic neurological condition (OR:1.41, 95%CI: 1.17, 1.69), chronic kidney disease (OR: 1.74, 95%CI: 1.35, 2.24), a BMI ≥40kg/m^2 (OR:2.89, 95%CI: 1.80, 4.64), a cancer diagnosis (OR: 2.77, 95%CI: 2.21, 3.47), or a comorbidity not listed within the ESF (OR: 2.24; 95%:1.91, 2.63). No significant associations were observed for those with chronic respiratory disease, chronic liver disease, asthma (requiring medication), an immunodeficiency disorder, or diabetes and risk of mortality (Table 1). A test for interaction found significant interactions with 5-year age and the following: chronic neurological disease ($p<0.001$), chronic respiratory disease ($p=0.006$), chronic kidney disease ($p=0.002$), chronic liver disease ($p=0.01$), immunodeficiency ($p<0.001$), diabetes ($p<0.001$), BMI ≥40kg/m^2 ($p<0.001$) and cancer ($p<0.001$).

3.3. Associations between underlying conditions and hospitalisation from COVID-19 among all confirmed cases within the study subset

Patterns of association between underlying conditions and risk of hospitalisation are shown in Table 2. There was a significant non-linear association between age and hospitalisation (X^2=452.67, $p<0.001$). All conditions, except chronic neurological disease and having a comorbidity not captured by the ESF were significantly associated with increased risk of hospitalisation (Table 2). Significant interactions were found between age and the following variables: chronic heart disease ($p=0.01$), chronic neurological disease ($p<0.001$), chronic kidney disease ($p<0.001$), diabetes ($p<0.01$), BMI ≥40kg/m^2 ($p=0.015$), cancer ($p<0.001$) and other comorbidity ($p<0.001$).

3.4. Associations between underlying conditions and ICU admission among those who were hospitalised from COVID-19 within the study subset

Table 3 shows the associations between the underlying conditions and ICU admission among confirmed cases of COVID-19 who were hospitalised (n=2,811). There was a significant non-linear association

Table 1
Associations between specific underlying conditions and mortality among all COVID-19 confirmed cases within the study subset (n=19,789) [a].

Risk factor	Alive (n= 18313)	Died (n=1476)	Unadjusted OR (95% CI)	Adjusted OR for age[1] (95% CI)	Adjusted OR[2] (95% CI)
Gender					
Male	7882	754 (8.73%)	1.38 (1.24, 1.54)	1.56 (1.38, 1.77)***	1.66 (1.43, 1.94)***
Female (*reference*)	10431	722 (6.47%)			
Chronic heart disease					
Yes	2055	645 (23.89%)	6.14 (5.49, 6.87)	1.63 (1.43, 1.85)***	1.28 (1.09, 1.50)**
No	16258	831 (4.86%)			
Chronic neurological condition					
Yes	713	511 (41.75%)	13.07 (11.47, 14.90)	2.64 (2.28, 3.07)***	1.41 (1.17, 1.69)**
No	17600	965 (5.20%)			
Chronic respiratory disease					
Yes	1824	259 (12.43%)	1.92 (1.67, 2.22)	1.20 (1.02, 1.42)*	1.09 (0.89, 1.33)
No	16489	1217 (6.87%)			
Chronic kidney disease					
Yes	384	174 (31.18%)	6.24 (5.17, 7.53)	1.99 (1.60, 2.47)***	1.74 (1.35, 2.24)***
No	17929	1302 (6.77%)			
Chronic liver disease					
Yes	134	28 (17.28%)	2.63 (1.74, 3.96)	1.44 (0.90, 2.31)	1.32 (0.80, 2.19)
No	18179	1448 (7.38%)			
Asthma (requiring medication)					
Yes	438	29 (6.21%)	0.82 (0.56, 1.20)	0.82 (0.53, 1.26)	0.82 (0.50, 1.35)
No	17875	1447 (7.49%)			
Immunodeficiency incl. HIV					
Yes	364	38 (9.45%)	1.30 (0.93, 1.83)	1.25 (0.85, 1.85)	0.87 (0.56, 1.35)
No	17949	1438 (7.42%)			
Diabetes					
Yes	999	225 (18.38%)	3.12 (2.67, 3.64)	1.40 (1.17, 1.67)**	1.08 (0.87, 1.33)
No	17314	1251 (6.74%)			
BMI $\geq$40kg/m^2					
Yes	267	31 (10.40%)	1.45 (1.00, 2.11)	2.48 (1.59, 3.87)**	2.89 (1.80, 4.64)***
No	18046	1445 (7.41%)			
Cancer / malignancy					2.77 (2.21, 3.47)***
Yes	514	233 (31.19%)	6.49 (5.50, 7.66)	2.58 (2.13, 3.13)***	
No	17799	1243 (6.53%)			
Other comorbidity					
Yes	3282	924 (21.97%)	7.67 (6.85, 8.58)	3.23 (2.84, 3.67)***	2.24 (1.91, 2.63)***
No	15031	552 (3.54%)			
Comorbidity unknown[$]				0.27 (0.21, 0.34)***	0.40 (0.29, 0.55)***
Yes	1496	93 (5.85%)	0.76 (0.61, 0.94)		
No	16817	1383 (7.60%)			
Residential care facility					
Yes	785	813 (50.88%)	27.38 (24.16, 31.03)	4.54 (3.93, 5.24)***	12.76 (10.31, 15.78)***
No	17528	663 (3.64%)			

[a]Age is modeled as a polynomial in the model and therefore odds ratios are not directly interpretable
[1]Adjusted OR, adjusted for age (linear, quadratic, cubic)
[2]Adjusted OR, adjusted for age (linear, quadratic, cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, BMI $\geq$40, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility and route of transmission.
[$]Where an underlying clinical condition was indicated but none of the conditions listed (and pregnancy) were reported. Odds ratios (OR), 95% confidence intervals (95%CI). P-value for overall association (Wald χ^2) *p<0.05; ** p<0.001; *** p<0.0001.

between age and ICU admission (X^2=216.88, p<0.001). Compared to those who did not have the condition, those with chronic heart disease, asthma (requiring medication), a BMI $\geq$40kg/m^2, or a comorbidity not listed on the ESF were significantly more likely, and those with chronic neurological disease significantly less likely to be admitted to ICU. There were significant interactions observed between age and chronic neurological disease (p=0.02), diabetes (p=0.04) and BMI $\geq$40kg/m^2 (p<0.001).

3.5. Associations between underlying conditions and mortality among those who were hospitalised from COVID-19 within the study subset

Associations between the underlying conditions examined and mortality among those who were hospitalised from COVID-19 are shown in Table 4. The non-linear association between age and mortality in hospitalised cases was non-significant (X^2=5.26, p=0.15) and a linear age term was used. Compared to those who were hospitalised and did not have the underlying condition, a significantly higher mortality risk was observed for those with a chronic neurological condition, chronic kidney disease, a BMI $\geq$40kg/m^2, a cancer diagnosis, or a comorbidity not listed on the ESF (Table 4). Those who were hospitalised and had asthma (requiring medication) had a lower risk of mortality compared to those without this underlying condition (Table 4). Significant interactions between age and BMI $\geq$40kg/m^2 (p<0.001) and between age and cancer (p<0.001) were found.

3.6. Validity and sensitivity analysis

The findings from the sensitivity analysis using the trimmed IPW were generally consistent with the results presented for analysis on all included cases (Supplementary Table 1). In most cases, the magnitude and significance of associations were similar between the IPW and main analysis presented, with some results strengthened in the IPW sensitivity analysis.

In addition, compared to those with no underlying conditions, increasing multimorbidity was associated with a significant linear increased risk of all outcomes examined (Supplementary Table 2A; with IPW Supplementary Table 2B).

Table 2
Associations between underlying conditions and hospitalisation from COVID-19 among all confirmed cases within the study subset (n=19,789)[a].

Risk factor	No hospitalisation (n=16978)	Hospitalised (n=2811)	Unadjusted OR (95% CI)	Adjusted OR for age[1] (95% CI)	Adjusted OR[2] (95% CI)
Gender					
Male	7020	1616 (18.71%)	1.92 (1.77, 2.08)	1.86 (1.71, 2.03)***	1.78 (1.62, 1.95)***
Female (*reference*)	9958	1195 (10.71%)			
Chronic heart disease					
Yes	1709	991 (36.70%)	4.87 (4.44, 5.33)	2.30 (2.08, 2.44)***	1.66 (1.48, 1.86)***
No	15269	1820 (10.65%)			
Chronic neurological condition					
Yes	866	358 (29.25%)	2.72 (2.38, 3.09)	1.01 (0.88, 1.17)	1.03 (0.88, 1.22)
No	16112	2453 (13.21%)			
Chronic respiratory disease					
Yes	1525	558 (26.79%)	2.51 (2.26, 2.79)	1.89 (1.68, 2.12)***	1.34 (1.18, 1.53)***
No	15453	2253 (12.72%)			
Chronic kidney disease					
Yes	281	277 (49.64%)	6.50 (5.47, 7.71)	3.40 (2.83, 4.08)***	2.24 (1.83, 2.75)***
No	16697	2534 (13.18%)			
Chronic liver disease					
Yes	94	68 (41.98%)	4.45 (3.25, 6.10)	2.77 (1.98, 3.89)***	1.57 (1.08, 2.30)*
No	16884	2743 (13.98%)			
Asthma (requiring medication)					
Yes	309	158 (33.83%)	3.21 (2.64, 3.91)	3.83 (3.08, 4.76)***	2.83 (2.23, 3.59)***
No	16669	2653 (13.73%)			
Immunodeficiency incl. HIV					
Yes	289	113 (28.11%)	2.42 (1.94, 3.02)	2.04 (1.61, 2.59)***	1.37 (1.05, 1.79)*
No	16689	2698 (13.92%)			
Diabetes					
Yes	766	458 (37.42%)	4.12 (3.64, 4.66)	2.27 (1.99, 2.59)***	1.60 (1.38, 1.85)***
No	16212	2353 (12.67%)			
BMI $\geq$40kg/m^2					
Yes	164	134 (44.97%)	5.14 (4.07, 6.48)	5.82 (4.50, 7.51)***	4.29 (3.27, 5.65)***
No	16814	2677 (13.73%)			
Cancer / malignancy					
Yes	396	351 (46.99%)	5.98 (5.14, 6.94)	2.88 (2.46, 3.38)***	2.39 (2.00, 2.84)***
No	16582	2460 (12.92%)			
Other comorbidity					
Yes	3102	1104 (26.25%)	2.89 (2.66, 3.15)	1.67 (1.52, 1.83)***	1.56 (1.41, 1.74)***
No	13876	1707 (10.95%)			
Comorbidity unknown[$]					
Yes	1430	159 (10.01%)	0.65 (0.55, 0.77)	0.44 (0.37, 0.52)***	1.14 (0.94, 1.38)
No	15548	2652 (14.57%)			
Residential care facility					
Yes	1365	233 (14.58%)	1.03 (0.90, 1.20)	0.25 (0.21, 0.29)***	0.28 (0.23, 0.34)***
No	15613	2578 (14.17%)			

[a]Age is modeled as a polynomial in the model and therefore odds ratios are not directly interpretable
[1]Adjusted OR, adjusted for age (linear, quadratic, cubic)
[2]Adjusted OR, adjusted for age (linear, quadratic, cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, BMI $\geq$40, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility and route of transmission.
[$]Where an underlying clinical condition was indicated but none of the conditions listed (and pregnancy) were reported. Odds ratios (OR), 95% confidence intervals (95%CI). P-value for overall association (Wald χ^2) *p<0.05; ** p<0.001; *** p<0.0001.

4. Discussion

This descriptive surveillance and nationally representative study for Ireland suggests that the presence of certain underlying conditions (specifically chronic heart disease and a BMI $\geq$40 kg/m^2) were associated with increased risk of mortality and hospitalisation among all confirmed COVID-19 cases and also with increased risk of ICU admission and mortality amongst COVID-19 confirmed cases who are hospitalised. Additionally, this study found that most of the chronic conditions captured in the ESF were significantly associated with increased risk of hospitalisation. Further, among those who were hospitalised, chronic heart disease, asthma (requiring medication) and BMI $\geq$40 kg/m^2 were associated with increased risk of ICU admission. Chronic neurological conditions, chronic kidney disease, BMI $\geq$40 kg/m^2 and cancer were all significantly associated with increased risk of death. These findings reflect international evidence, [16] and shows confirmatory and consistent findings at a country level that the presence of underlying conditions is associated with worse COVID-19 infection outcomes [16].

Our findings of elevated risk of death and hospitalisation among men in Ireland is consistent with international evidence of gender imbalance among outcomes of COVID-19 infected cases. Among our study population, 44% were men, which is lower than observed in a recent meta-analysis of 57 studies that found the prevalence of COVID-19 to be 55% among men [17]. As shown in a systematic review of sixteen studies, including studies from China, United States, Italy, UK and Spain, men had increased disease severity including hospitalisation and ICU admission compared to women [18]. Although it is not fully understood why men are more susceptible to a severe disease trajectory many factors have been proposed that may underlie these differences including immunological differences, elevated expression of certain factors including angiotensin-converting enzyme 2, differences in hormones (e.g., oestrogen) and also social and behavioural differences [19,20]. It is likely, however, that these differences are multifactorial and complex [19,21].

As highlighted by the European Centre for Disease Prevention and Control (ECDC), within their COVID-19 surveillance report, the top three underlying conditions among fatal COVID-19 cases are cardiac

Table 3
Associations between underlying conditions and ICU admission among those who were hospitalised from COVID-19 within the study subset (n=2,811)[a].

Risk factor	No ICU admission but hospitalised (n=2373)	ICU admission (n=438)	Unadjusted OR (95% CI)	Adjusted OR for age[1] (95% CI)	Adjusted OR[2] (95% CI)
Gender					
Male	1314	302 (18.69%)	1.79 (1.44, 2.23)	1.61 (1.28, 2.02)***	1.53 (1.19, 1.97)**
Female (*reference*)	1059	136 (11.38%)			
Chronic Heart Disease					
Yes	775	216 (21.80%)	2.01 (1.63, 2.47)	2.90 (2.29, 3.68)***	2.48 (1.90, 3.24)***
No	1598	222 (12.20%)			
Chronic Neurological condition					
Yes	338	20 (5.59%)	0.29 (0.18, 0.46)	0.38 (0.24, 0.62)***	0.35 (0.21, 0.60)**
No	2035	418 (17.04%)			
Chronic respiratory disease					
Yes	451	107 (19.18%)	1.38 (1.08, 1.75)	1.47 (1.14, 1.90)*	0.99 (0.73, 1.34)
No	1922	331 (14.69%)			
Chronic Kidney Disease					
Yes	237	40 (14.44%)	0.91 (0.64, 1.29)	1.10 (0.76, 1.60)	1.00 (0.66, 1.52)
No	2136	398 (15.71%)			
Chronic Liver Disease					
Yes	54	14 (20.59%)	1.42 (0.78, 2.58)	1.10 (0.59, 2.04)	0.86 (0.43, 1.72)
No	2319	424 (15.46%)			
Asthma (requiring medication)					
Yes	108	50 (31.65%)	2.70 (1.90, 3.84)	2.63 (1.80, 3.84)***	2.31 (1.47, 3.63)**
No	2265	388 (14.62%)			
Immunodeficiency incl. HIV					
Yes	87	26 (23.01%)	1.66 (1.06, 2.60)	1.38 (0.86, 2.20)	1.46 (0.88, 2.43)
No	2286	412 (15.27%)			
Diabetes					
Yes	347	111 (24.24%)	1.98 (1.55, 2.53)	1.94 (1.50, 2.52)***	1.27 (0.93, 1.72)
No	2026	327 (13.90%)			
BMI $\geq$40kg/m^2					
Yes	52	82 (61.19%)	10.28 (7.14, 14.81)	7.91 (5.39, 11.59)***	7.53 (4.94, 11.48)***
No	2321	356 (13.30%)			
Cancer / malignancy					
Yes	301	50 (14.25%)	0.89 (0.65, 1.22)	0.91 (0.65, 1.27)	0.90 (0.62, 1.30)
No	2072	388 (15.77%)			
Other comorbidity					
Yes	894	210 (19.01%)	1.52 (1.24, 1,87)	1.81 (1.45, 2.25)***	1.75 (1.37, 2.24)***
No	1479	228 (13.36%)			
Comorbidity unknown[$]					
Yes	155	4 (2.52%)	0.13 (0.05, 0.36)	0.17 (0.06, 0.46)**	0.38 (0.13, 1.06)
No	2218	434 (16.37%)			
Residential care facility					
Yes	224	9 (3.86%)	0.20 (0.10, 0.40)	0.35 (0.17, 0.69)*	0.58 (0.27, 1.28)
No	2149	429 (16.64%)			

[a]Age is modeled as a polynomial in the model and therefore odds ratios are not directly interpretable
[1]Adjusted OR, adjusted for age (linear, quadratic, cubic)
[2]Adjusted OR, adjusted for age (linear, quadratic, cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, BMI $\geq$40, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility and route of transmission.
[$]Where an underlying clinical condition was indicated but none of the conditions listed (and pregnancy) were reported. Odds ratios (OR), 95% confidence intervals (95%CI). P-value for overall association (Wald χ^2) *p<0.05; ** p<0.001; *** p<0.0001.

disorder, diabetes, and cancer / malignancy [16]. Among our study population, we also observed a strong association for mortality among those with a cancer diagnosis. Of note, 4.9% of fatal cases had a pre-existing kidney-related condition (renal disease), for which we also observed an association for higher risk of mortality overall and among those hospitalised.

This study examined many underlying conditions. Across all of the outcomes examined, a BMI $\geq$40 kg/m^2 was associated with higher risk of death, hospitalisation, and ICU admission. Throughout the pandemic, the pre-existing worldwide epidemic of obesity has been recognised as a significant and important risk factor for COVID-19 infection and for worse outcomes [22,23]. Our findings also support prior studies of an association between obesity and higher risk of poorer prognostic outcomes [23,24]. Of note, most prior studies included in a recent systematic review and meta-analysis classified obesity as those with a BMI $\geq$ 30 kg/m^2 [23]. The present study focused on the morbidly obese group with a BMI $\geq$ 40 kg/m^2, which accounted for 1.5% of the study population. Similar associations for morbid obesity were observed within a Spanish population based cohort study, particularly among younger age groups (<50 years), where a similar magnitude for disease severity was found to that of aging [25].

Strengths of this study include the population representative sample from Ireland, the inclusion of only laboratory confirmed cases, the relatively large sample size, and the large number of underlying conditions for which information was collected. This descriptive study presents findings consistent with prior reports and is the first to examine these associations in an Irish setting. A strength of this study is that the analysis is based on data from the national surveillance system in Ireland. Therefore, the results represent findings generalisable to the total population, including community and hospital cohorts, unlike many prior studies that have focused on individual hospital settings or have shown these associations at a local level [5-8]. Further, this study offers the opportunity for findings relating to mortality information that can be compared with other European regions e.g. settings that were/were not overwhelmed by COVID-19. Limitations include the lack of some information in relation to unknown or missing underlying conditions and the absence of

Table 4
Associations between underlying conditions and mortality among those who were hospitalised from COVID-19 within the study subset (n=2,811).

Risk factor	Hospitalised and alive (n=2119)	Hospitalised and died (n=692)	Unadjusted OR (95% CI)	Adjusted OR for age[1] (95% CI)	Adjusted OR[2] (95% CI)
Gender					
Male	1195	421 (26.05%)	1.20 (1.01, 1.43)	1.34 (1.11, 1.65)*	1.38 (1.12, 1.71)*
Female (*reference*)	924	271 (21.68%)			
Chronic heart disease					
Yes	649	342 (34.51%)	2.21 (1.86, 2.64)	1.30 (1.07, 1.58)*	1.23 (0.99, 1.54)
No	1470	350 (19.23%)			
Chronic neurological condition					
Yes	198	160 (44.69%)	2.92 (2.32, 3.67)	1.75 (1.37, 2.24)***	1.37 (1.04, 1.81)*
No	1921	532 (21.69%)			
Chronic respiratory disease					
Yes	391	167 (29.93%)	1.41 (1.14, 1.73)	1.16 (0.92, 1.45)	1.19 (0.92, 1.53)
No	1728	525 (23.30%)			
Chronic kidney disease					
Yes	157	120 (43.32%)	2.62 (2.03, 3.38)	1.91 (1.45, 2.53)***	1.75 (1.29, 2.38)**
No	1962	572 (22.57%)			
Chronic liver disease					
Yes	47	21 (30.88%)	1.38 (0.82, 2.33)	1.50 (0.86, 2.63)	1.30 (0.72, 2.34)
No	2072	671 (24.46%)			
Asthma (requiring medication)					
Yes	138	20 (12.66%)	0.43 (0.27, 0.69)	0.52 (0.31, 0.87)*	0.49 (0.28, 0.85)*
No	1981	672 (25.33%)			
Immunodeficiency incl. HIV					
Yes	85	28 (24.78%)	1.01 (0.65, 1.56)	1.24 (0.77, 2.00)	0.91 (0.54, 1.55)
No	2034	664 (24.61%)			
Diabetes					
Yes	333	125 (27.29%)	1.18 (0.94, 1.48)	1.00 (0.78, 1.27)	0.84 (0.64, 1.10)
No	1786	567 (24.10%)			
BMI $\geq$40kg/m^2					
Yes	104	30 (22.39%)	0.88 (0.58, 1.33)	1.81 (1.14, 2.86)*	2.19 (1.34, 3.56)*
No	2015	662(24.73%)			
Cancer / malignancy					
Yes	203	148 (42.17%)	2.57 (2.04, 3.24)	2.11 (1.63, 2.71)***	2.15 (1.63, 2.83)***
No	1916	544 (22.11%)			
Other comorbidity					
Yes	699	405 (36.68%)	2.87 (2.40, 3.42)	2.30 (1.90, 2.79)***	2.05 (1.65, 2.55)***
No	1420	287 (16.81%)			
Comorbidity unknown[$]					
Yes	120	39 (24.53%)	1.00 (0.69, 1.44)	0.62 (0.41, 0.92)*	0.96 (0.59, 1.58)
No	1999	653 (24.62%)			
Residential care facility					
Yes	83	150 (62.38%)	6.79 (5.11, 9.02)	3.80 (2.79, 5.17)***	5.02 (3.46, 7.30)***
No	2036	542 (21.02%)			

[a]

[1]Adjusted OR, adjusted for age (linear)
[2]Adjusted OR, adjusted for age (linear), chronic heart disease, chronic neurological disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, asthma (requiring meds), immunodeficiency, diabetes, BMI $\geq$40, cancer, other comorbidity, unknown comorbidity, community health office, residential care facility and route of transmission.
[$]Where an underlying clinical condition was indicated but none of the conditions listed (and pregnancy) were reported. Odds ratios (OR), 95% confidence intervals (95%CI). P-value for overall association (Wald χ^2) *p<0.05; ** p<0.001; *** p<0.0001.

information gathered on severity of the underlying conditions. These data aim to capture risks associated with mortality and hospitalisation since the beginning of the pandemic. However, as the pandemic evolved and knowledge about COVID-19 and coronavirus increased, both testing criteria and case definitions changed in Ireland. This is reflected in changes within the ESF, which occurred during the study period. Therefore, it is likely that variation in age groups and symptom severity groups were targeted by testing guidelines at different time points over the study period. However, more cases from a specific risk group (e.g., those in residential facilities) may have been detected during certain time points within the study. Additionally, while the ESF aimed to capture detailed information on characteristics of those with a confirmed diagnosis of COVID-19, the forms were not always completed in full, resulting in missing data for underlying conditions for almost a quarter of all confirmed cases which likely resulted in potential bias in the reported results. However, in sensitivity analysis examining the impact of missing data, the overall findings and conclusions were broadly similar. An additional limitation of the current study was that no clinical data such as oxygen saturation, urea level, and C-reactive protein was captured or reported; data which has been important in the development of a COVID-19 mortality risk score [26]. Further, there are likely to be a number of other characteristics that were not captured in the ESF and, therefore, could not be accounted for in the analysis, which may have resulted in residual bias. While these limitations must be acknowledged, it is important to highlight that this study was not designed to estimate causal effects. Further, some of the associations with less common underlying conditions may have been underpowered in our study. In addition, this analysis is based on data provided by the HPSC at time of release. It is possible however, that there is the potential for misclassification of some information, given ongoing system updates to data ascertainment that occurred during the course of the pandemic. However, any misclassification, is expected to be minimal. A further limitation relates to differential follow-up and although follow-up

continued for at least 6 weeks after the last confirmed case in the study, the differential follow-up of some cases, may have introduced bias into the analysis.

While knowledge on COVID-19 continues to expand, conducting descriptive and surveillance epidemiological studies among those who have tested positive for COVID-19, particularly from a national population setting, will continue to provide insights into the pathogenesis of the disease. Findings may inform the development of tools to predict those at highest risk of mortality, hospitalisation, and ICU admission [26]. There are ongoing efforts examining clinical data to develop predictive tools associated with prognosis [27]. Currently, while vaccines are being administered or are under development or review by regulators, all efforts must be made to identify the most vulnerable to infection and better identify those at highest risk of adverse outcomes, particularly among the wider general population. As much of the world is now experiencing subsequent resurgences in COVID-19 incidence, it is recognised that the patterns of current waves may not reflect the first wave. For example, in relation to the demographics of those infected, higher incidence has been observed among younger age groups than was experienced previously [28]. Future studies examining risk factors associated with disease severity in confirmed cases and within the resurgent time-frame will be needed to further characterise the coronavirus disease within the population setting.

In conclusion, in a nationally representative sample of COVID-19 confirmed cases from Ireland, this study identified patient level underlying conditions associated with disease severity including mortality, hospitalisation, and ICU admission. Application of this knowledge is required in a clinical setting to identify those at elevated risk who would benefit from preventive intervention opportunities, including in vaccination programmes. Understanding factors associated with adverse outcomes will help to improve the recognition of those at high-risk of mortality, hospital and ICU admission following infection. Further, additional understanding of those who experience the most severe prognosis may inform the development of clinical strategies to prevent further adverse events and inform opportunities to reduce the burden of coronavirus disease, should future resurgences in infections occur.

Author contributions

KEB, AO, MOL, MF, JOD, MM, LOC and JC designed the study and analysis plan. AO, MOL and KEB prepared the data for analysis. KEB completed the statistical analysis. MM and KEB drafted the initial and final versions of the manuscript. All authors critically reviewed manuscript drafts and approved the final draft of the manuscript for submission.

Data sharing statement

The dataset and codes used and analysed for this study are available upon reasonable request and following formal application to the HPSC.

Funding

This study was supported by the Health Service Executive, Health Protection Surveillance Centre. KEB and MM are funded by the Health Research Board (RL-15-1579 and EIA-2019-012 respectively).

Declaration of Competing Interest

All authors have no conflict of interest to declare.

Acknowledgements

We would like to acknowledge the work of the Departments of Public Health in Ireland and in particular, colleagues involved in the CIDR and COVID-19 Epidemiology teams. We express our thanks to all those who are participating in the collection of data which include staff in HSE COVID-19 Contact Management Programme (CMP), ICU units, notifying clinicians, laboratory staff, public health doctors, nurses, surveillance scientists, microbiologists and administrative colleagues.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100097.

References

[1] World Health Organization. Coronavirus disease (COVID-19) pandemic. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
[2] World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report –46. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04adf_.
[3] Health Protection Surveillance Centre (HPSC) Health Service Executive (HSE). COVID-19 Cases in Ireland - infographic prepared by HPSC on 15/01/2021. 2020. https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/casesinireland/epidemiologyofcovid-19inireland/COVID19%20Daily%20infographic.pdf. Accessed on 18 January 2021.
[4] Working group for the surveillance and control of COVID-19 in Spain. The first wave of the COVID-19 pandemic in Spain: characterisation of cases and risk factors for severe outcomes, as at 27 April 2020. Euro Surveill 2020;25(50).
[5] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
[6] Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M, et al. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the italian society of hypertension. Hypertension 2020;76(2):366–72.
[7] Atkins JL, Masoli JAH, Delgado J, Pilling LC, Kuo CL, Kuchel GA, et al. Preexisting comorbidities predicting COVID-19 and mortality in the UK biobank community cohort. J Gerontol A Biol Sci Med Sci 2020;75(11):2224–30.
[8] Nystad W, Hjellvik V, Larsen IK, Ariansen I, Helland E, Johansen KI, et al. Underlying conditions in adults with COVID-19. Tidsskr Nor Laegeforen 2020;140(13).
[9] Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Med Virol. 2020.
[10] Keller KG, Reangsing C, Schneider JK. Clinical presentation and outcomes of hospitalized adults with COVID-19: a systematic review. J Adv Nurs 2020;76(12):3235–57.
[11] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007;147(8):573–7.
[12] Health Protection Surveillance Centre (HPSC) Health Service Executive (HSE). Notifiable Diseases 2020 [Available from: https://www.hpsc.ie/notifiablediseases/listofnotifiablediseases/.
[13] Health Protection Surveillance Centre (HPSC) health service executive (HSE). COVID-19 interim case definition 2020. Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/casedefinitions/covid-19interimcase-definitionforireland/.
[14] World Health Organization. International guidelines for certification and classification (coding) of COVID-19 as cause of death. 2020.
[15] Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res 2013;22(3):278–95.
[16] European centre for disease prevention and control. COVID-19 Sueveillance report https://covid19-surveillance-report.ecdc.europa.eu/#weekly_surveillance_summary; 2020.
[17] Abate BB, Kassie AM, Kassaw MW, Aragie TG, Masresha SA. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. BMJ Open 2020;10(10):e040129.
[18] Kelada M, Anto A, Dave K, Saleh SN. The role of sex in the risk of mortality from COVID-19 amongst adult patients: a systematic review. Cureus 2020;12(8):e10114.
[19] Bwire GM. Coronavirus: why men are more vulnerable to Covid-19 Than Women? SN Compr Clin Med. 2020:1-3.
[20] Haitao T, Vermunt JV, Abeykoon J, Ghamrawi R, Gunaratne M, Jayachandran M, et al. COVID-19 and sex differences: mechanisms and biomarkers. Mayo Clin Proc 2020;95(10):2189–203.
[21] Pirhadi R, Sinai Talaulikar V, Onwude J, Manyonda I. Could estrogen protect women from COVID-19? J Clin Med Res 2020;12(10):634–9.
[22] de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of

General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis 2020;20(9):1034–42.
[23] Huang Y, Lu Y, Huang YM, Wang M, Ling W, Sui Y, et al. Obesity in patients with COVID-19: a systematic review and meta-analysis. Metabolism 2020;113:154378.
[24] Peters SAE, MacMahon S, Woodward M. Obesity as a risk factor for COVID-19 mortality in women and men in the UK biobank: Comparisons with influenza/pneumonia and coronary heart disease. Diabetes Obes Metab. 2020.
[25] Fresan U, Guevara M, Elia F, Albeniz E, Burgui C, Castilla J, et al. Independent role of morbid obesity as a risk factor for COVID-19 hospitalization: a Spanish population-based cohort study. Obesity (Silver Spring). 2020.
[26] Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C Mortality Score. BMJ 2020;370:m3339.
[27] McElvaney OJ, Hobbs BD, Qiao D, McElvaney OF, Moll M, McEvoy NL, et al. A linear prognostic score based on the ratio of interleukin-6 to interleukin-10 predicts outcomes in COVID-19. EBioMedicine 2020;61:103026.
[28] Health Protection Surveillance Centre (HPSC) Health Service Executive (HSE). Epidemiology of COVID-19 in Ireland weekly reports 2020. Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/surveillance/epidemiologyofcovid-19inirelandweeklyreports/.