Comorbid Chronic Diseases and Ventilatory Support in COVID-19 Hospitalisations

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Abstract

Aim
COVID-19, a historic pandemic, exhibits varying severities among individuals. This retrospective study aimed to investigate how chronic diseases influence outcomes in hospitalised patients with COVID-19.

Methods
We reviewed patient records from three northwest Irish hospitals encompassing COVID-19 admissions from February 2020 to May 2021. The data included demographics, chronic diseases (e.g. diabetes and hypertension), body mass index, and smoking status. The outcomes assessed included hospital stay duration, need for non-invasive ventilation (NIV), invasive mechanical ventilation, tracheostomy, intensive care unit stay length, and mortality.

Results
Among a total of 1,748 patients, with a mean age of 66 years, prevalent comorbidities included hypertension in 807 patients (46.2%), obesity in 568 patients (38.4%), type 2 diabetes in 385 patients (22.0%), coronary artery disease in 326 patients (18.6%), and chronic kidney disease in 281 patients (16.1%). Patients with type 2 diabetes mellitus (P<.001), obesity (P<.001), and COPD (P=.01) had elevated odds of requiring NIV. Additionally, older age (P<.001), coronary artery disease (P=.002), and heart failure (P=.042) increased mortality risk.

Hospitalised COVID-19 patients face higher mortality risks due to age, coronary artery disease, and heart failure. Moreover, type 2 diabetes, chronic obstructive pulmonary disease (COPD),
Introduction

The world has been dealing with the COVID-19 pandemic since 2019. It has caused significant morbidity and more than six million deaths globally. Along with its economic and social impacts, COVID-19 has increased the burden on healthcare settings and disrupted essential health services. The severity of the COVID-19 disease ranges from asymptomatic to fatal. A report from China showed that almost 81% of COVID-19 patients had only mild disease during the first wave of the pandemic. Even with a 4.4% hospitalisation rate and 0.5% intensive care unit admission rate among confirmed COVID-19 cases, the pandemic exerted a significant burden on the healthcare delivery systems.

Many factors that contribute to the severity of COVID-19 have been identified since the beginning of the pandemic. A report by the Chinese Centre for Disease Control and Prevention (CCDC) on the first wave of COVID-19 highlighted that existing comorbidities, including cardiovascular disease, hypertension, diabetes mellitus, chronic respiratory disease, and cancer, were associated with higher mortality in COVID-19 patients. A recent meta-analysis of 34 studies with a pooled sample of 19,156 patients also revealed that existing cardiovascular disease was associated with severe outcomes and mortality in COVID-19 patients. Hypertension, one of the most prevalent comorbidities among COVID-19 patients, also increases the risk of mortality and severe disease.

Metabolic diseases such as obesity and diabetes mellitus have also been identified as risk factors for more severe diseases among COVID-19 patients. Moreover, a large meta-analysis involving 186 studies and 1.3 million patients reported that diabetes mellitus, obesity, hypertension, and smoking were associated with higher mortality in COVID-19 patients. The island of Ireland has experienced an unprecedented public health emergency due to COVID-19. There have been approximately 1.5 million positive COVID-19 cases in the Republic of Ireland (ROI) and more than 700,000 cases in the Northern Ireland (NI) Department of Health. This paper reports a retrospective study on the impact of comorbidities on the severity and outcomes of COVID-19 was conducted at three major hospitals in Ireland and Northern Ireland.

Methods

This retrospective study assessed the effect of comorbid chronic diseases on hospitalised patients diagnosed with COVID-19. The study was conducted at three major acute hospitals.
in Ireland: Letterkenny University Hospital (LUH) in the Republic of Ireland (ROI), Altnagelvin Hospital (AH), and Southwest Acute Hospital (SWAH) in Northern Ireland (NI), United Kingdom. LUH serves a catchment area encompassing most of County Donegal in the Northwest of Ireland, catering to over 140,000 people. AH and SWAH cover the western region of NI, serving approximately 300,000 residents.

All adult patients admitted to these hospitals from the onset of the COVID-19 pandemic until 31 May 2021 with laboratory-confirmed COVID-19 diagnoses, either at admission or during their hospital stay, were included. Admissions related to pregnancy and maternity were excluded from the study.

Ethical approval for this study was granted by the LUH Research Ethics Committee (LUHREC CA 26/03/2021), Office of Research Ethics Committees Northern Ireland (REC Ref: 21/EE/0075), and Atlantic Technological Institute (formerly Letterkenny Institute of Technology) (IREC 27/03/2021).

The list of inpatients with confirmed COVID-19 diagnoses during the study period was obtained from participating hospitals. Research nurses meticulously extracted relevant data by reviewing hospitals’ online databases and paper patient charts. Data were anonymised at the point of collection.

Data collected included patient characteristics such as age, gender, geographic location of residence, admission month and year, smoking status, and comorbidities. The comorbidities of interest included diabetes mellitus types 1 and 2 (DM Type-1/DM Type-2), hypertension, coronary artery disease (CAD), heart failure (HF), obesity, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and asthma. Additionally, parameters related to severity and outcomes, such as length of hospital stay (LoS-H), length of ICU stay (LoS-ICU), need for non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), tracheostomy, and mortality, were also recorded.

Results

Continuous variables are presented as mean ± standard deviation, while categorical variables are shown as counts and percentages. To assess the independence of variables, Pearson’s chi-squared test and Fisher’s exact test were employed for count data. Univariate linear regression was used to identify potentially significant variables for further analysis in multivariate logistic regression using a threshold of $P \leq 0.1$. We conducted multivariate logistic regression, iteratively refining the model by removing variables with high degrees of missing data and optimising the model performance and assumptions. Statistical analyses were performed using R version 4.2.0, using the Caret and Information Value packages for model
generation statistics and assumption testing. Data visualisation was accomplished using the ggplot2 and ggsplot packages.

The baseline characteristics of the 1748 consecutive COVID-19 patients admitted to the study sites are summarised in Table 1. Altnagelvin Hospital (AH) contributed nearly half of the sample (49.8%), followed by Letterkenny University Hospital (LUH) (30.9%) and Southwest Acute Hospital (SWAH) (19.3%). Males comprised 57% of the sample, with an average age of 66.45 ± 16.91 years. Notably, the SWAH had an older cohort, with an average age of 70.34 ± 16.54 years. Approximately half of the patients resided in urban areas, closely followed by those from accessible rural (AR) areas (39.6%). Geographic variations were evident, with 69.7% of AH’s patients from urban areas and no patients from remote rural (RR) areas. SWAH had <1% of RR patients, with the majority from AR area (62.6%). In contrast, LUH had nearly one-third of its patients from RR areas and only about a quarter from urban communities (26.7%).

Data on smoking status and comorbidities (DM Types 1 and 2, hypertension, CAD, HF, obesity, CKD, COPD, and asthma) were collected to assess their impact on COVID-19 severity and outcomes. More than half (53.1%) of the sample had never smoked, while 36.1% were ex-smokers, constituting the majority (89.2%) of the sample. Smoking status was not documented in 171 (9.8%) patients. Hypertension was the most prevalent comorbidity (46.2%), followed by obesity (38.4%) and DM Type-2 (22%). CAD and CKD were present in 18.7% and 16.1% of the patients, respectively. COPD and asthma were present in just over 10% of the sample, while HF (9.2%) and DM Type-1 (1.8%) were less prevalent. Data on obesity were missing for 269 (15.4%) patients.

The average hospital stay (LoS-H) was 12.42 ± 16.59 days across the sample. AH had the lowest mean LoS-H (9.45 ± 11.75 days), while SWAH and LUH had similar mean LoS-H (approximately 15 days). ICU admission was required in 7.9% of COVID-19 patients. LUH had the highest ICU admission rate (10.39%), whereas AH and SWAH accounted for 7.1% of patients admitted to the ICU. The mean LoS-ICU was 12.79 ± 18 days. Non-invasive ventilation (NIV) was needed in 15% of the patients, and 4.8% required invasive mechanical ventilation (IMV). Tracheostomy was required for only 13 patients (0.8%). The mortality rate was 14.8% in the sample, with the highest rate in SWAH (23.1%), followed by AH (13%), and LUH (12.5%).
**Table 1: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total N (%)</th>
<th>AH n (%)</th>
<th>SWAH n (%)</th>
<th>LUH n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>66.45 (16.9)</td>
<td>64.91 (16.7)</td>
<td>70.34 (16.5)</td>
<td>66.5 (17.1)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>997 (57%)</td>
<td>484 (55.6%)</td>
<td>183 (54.3%)</td>
<td>330 (61.1%)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>751 (43%)</td>
<td>387 (44.4%)</td>
<td>154 (45.7%)</td>
<td>210 (38.9%)</td>
</tr>
<tr>
<td><strong>Geographic Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>874 (50%)</td>
<td>607 (69.7%)</td>
<td>123 (36.5%)</td>
<td>144 (26.7%)</td>
</tr>
<tr>
<td>Accessible Rural</td>
<td>692 (39.6%)</td>
<td>264 (30.3%)</td>
<td>211 (62.6%)</td>
<td>217 (40.2%)</td>
</tr>
<tr>
<td>Remote Rural</td>
<td>182 (10.4%)</td>
<td>0 (0%)</td>
<td>3 (0.9%)</td>
<td>179 (33.2%)</td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>170 (10.8%)</td>
<td>117 (14.5%)</td>
<td>18 (5.9%)</td>
<td>35 (7.5%)</td>
</tr>
<tr>
<td>No</td>
<td>838 (53.1%)</td>
<td>450 (55.7%)</td>
<td>152 (49.8%)</td>
<td>236 (50.9%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>569 (36.1%)</td>
<td>241 (29.8%)</td>
<td>135 (44.3%)</td>
<td>193 (41.6%)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM 1</td>
<td>32 (1.8%)</td>
<td>23 (2.6%)</td>
<td>1 (0.3%)</td>
<td>8 (1.5%)</td>
</tr>
<tr>
<td>DM 2</td>
<td>385 (22%)</td>
<td>192 (22%)</td>
<td>89 (26.4%)</td>
<td>104 (19.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>807 (46.2%)</td>
<td>365 (41.9%)</td>
<td>187 (55.5%)</td>
<td>255 (47.2%)</td>
</tr>
<tr>
<td>CAD</td>
<td>326 (18.7%)</td>
<td>163 (18.7%)</td>
<td>57 (16.9%)</td>
<td>106 (19.6%)</td>
</tr>
<tr>
<td>HF</td>
<td>160 (9.2%)</td>
<td>67 (7.7%)</td>
<td>37 (10%)</td>
<td>56 (10.4%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>568 (38.4%)</td>
<td>275 (36.3%)</td>
<td>126 (45.7%)</td>
<td>167 (37.4%)</td>
</tr>
<tr>
<td>CKD</td>
<td>281 (16.1%)</td>
<td>119 (13.7%)</td>
<td>100 (29.7%)</td>
<td>62 (11.5%)</td>
</tr>
<tr>
<td>COPD</td>
<td>223 (12.8%)</td>
<td>93 (10.7%)</td>
<td>57 (16.9%)</td>
<td>73 (13.5%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>212 (12.1%)</td>
<td>105 (12.1%)</td>
<td>43 (12.8%)</td>
<td>64 (11.9%)</td>
</tr>
<tr>
<td><strong>Outcome Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LoS H*</td>
<td>12.42 (16.6)</td>
<td>9.45 (11.8)</td>
<td>15.28 (23.9)</td>
<td>15.4 (16.8)</td>
</tr>
<tr>
<td>ICU Admission</td>
<td>138 (7.9%)</td>
<td>58 (6.7%)</td>
<td>24 (7.1%)</td>
<td>56 (10.4%)</td>
</tr>
<tr>
<td>LoS ICU*</td>
<td>12.79 (18)</td>
<td>15.84 (25.6)</td>
<td>10.62 (8.8)</td>
<td>10.55 (9)</td>
</tr>
<tr>
<td>NIV</td>
<td>256 (15%)</td>
<td>143 (16.8%)</td>
<td>30 (9.3%)</td>
<td>83 (15.6%)</td>
</tr>
<tr>
<td>IMV</td>
<td>83 (4.8%)</td>
<td>28 (3.3%)</td>
<td>14 (4.2%)</td>
<td>41 (7.6%)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>13 (0.8%)</td>
<td>4 (0.5%)</td>
<td>2 (0.6%)</td>
<td>7 (1.3%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>258 (14.8%)</td>
<td>113 (13%)</td>
<td>78 (23.1%)</td>
<td>67 (12.5%)</td>
</tr>
</tbody>
</table>

*Values are in Mean (SD)
Multivariate logistic regression analysis was performed to assess the impact of patient characteristics and comorbid chronic diseases on mortality and NIV, IMV, and tracheostomy requirements.

Among the admitted COVID-19 patients, 256 (15%) required non-invasive ventilation (NIV). Univariate analysis revealed significant associations between NIV requirements and urban residence, ex-smoker status, and the presence of DM Type-2, obesity, COPD, and asthma. Even after adjusting for major covariates in the multivariate analysis, DM Type-2 exhibited the highest odds of requiring NIV (adjusted OR=2.8, 95% CI=1.65-4.72, P<.001). Obesity (adjusted OR=2.2, 95% CI=1.35-3.45, P<.001) and COPD (adjusted OR=2.4, 95% CI=1.22-4.55, P=.01) also independently increased the likelihood of requiring NIV.

The sole factor associated with an increased risk of death was advancing age (adjusted OR=1.1, 95% CI=1.08-1.11, P<.001) (Figure 1). Repeating the analysis after excluding 76 cases with missing values revealed that CAD (adjusted OR=1.8, 95% CI=1.23-2.53, P=.001) and HF (adjusted OR=1.6, 95% CI=1.01-2.46, P=.04) were also linked to an elevated risk of mortality.

Figure 1: Distribution of age across mortality

No patient-specific factor exhibited a statistically significant association with the need for IMV. However, when comparing the three study sites, patients admitted to Letterkenny University Hospital (LUH) had higher odds of requiring IMV than those admitted to Altnagelvin
Hospital (AH) and Southwest Acute Hospital (SWAH) (adjusted OR=4.0, 95% CI=1.24-14.68, P=.02).

Tracheostomy was a relatively rare intervention, with only 13 patients requiring it in the entire sample. Notably, patients with COPD had an elevated likelihood of undergoing tracheostomy (adjusted OR=12.74, 95% CI=1.04-203.37, P=0.05) even after adjusting for other key variables.

Discussion

COVID-19 has had a profound impact worldwide, affecting over 500 million individuals. However, the disease is not severe in most cases. Sun and colleagues\textsuperscript{11} reported that almost 90% of COVID-19 patients had a fever and 72% had a cough, but only 14.8% of them developed acute respiratory distress syndrome (ARDS). In this study, we aimed at finding the impact of comorbid chronic diseases on the severity and outcome of COVID-19 and our main findings are 1) DM Type-2, COPD, and obesity increase the risk of the requirement of NIV support, 2) increasing age, CAD, and HF increase the risk of death, and 3) existing COPD can increase the odds of having tracheostomy in COVID-19 patients admitted in hospitals.

The factors associated with severe COVID-19 have been widely reported. The World Health Organization (WHO) Working Group on the Clinical Characterisation and Management of COVID-19 infection classified COVID-19 disease requiring high flow oxygen (HFO), non-invasive ventilation (NIV), or intubation and invasive mechanical ventilation (IMV) as severe disease\textsuperscript{12}. A substantial meta-analysis by Booth and colleagues\textsuperscript{13}, encompassing a vast cohort of over 17 million patients, indicated that active cancer was associated with a higher risk of severity. In contrast, diabetes, hypertension, and chronic kidney disease (CKD) did not demonstrate significant associations with COVID-19 severity. However, previous studies have highlighted various comorbidities, including COPD\textsuperscript{14}, dyslipidaemia\textsuperscript{15}, DM\textsuperscript{16}, cerebrovascular disease\textsuperscript{17}, hypertension\textsuperscript{18}, CAD\textsuperscript{19}, HF\textsuperscript{20}, and CKD\textsuperscript{21} as risk factors for severe COVID-19. Our study adopted a unique approach by identifying comorbidities specifically associated with an increased likelihood of requiring NIV, IMV, or tracheostomy. We found that obesity, COPD, and DM Type-2 were independent risk factors for severe disease requiring NIV, and COPD was also correlated with a higher risk of tracheostomy. Notably, multivariate logistic regression analysis did not reveal significant associations between IMV and the studied comorbidities or demographic variables.

The impact of comorbidities on mortality in COVID-19 patients has been widely studied; however, to the best of our knowledge, this is the first study to report on the impact of COVID-19 among hospitalised people in Ireland. A systematic review and meta-analysis of 14 studies with a pooled sample of 4659 hospitalised COVID-19 patients, reported that hypertension, CAD, and diabetes were associated with a higher risk of death\textsuperscript{22}. In comparison, a meta-
analysis involving 20 studies and 15,408 patients performed by Xiang et al.\textsuperscript{23} produced slightly different results. They found that respiratory disease, CKD, and cancer also increased the death risk in hospitalised COVID-19 patients, along with hypertension, CAD, and diabetes. In contrast, a larger meta-analysis of 45 studies with a pooled sample of 18,300 patients found only age and diabetes as risk factors for higher mortality among in-hospital COVID-19 patients\textsuperscript{24}. Interestingly, the above-mentioned studies reported many disparities in their findings, which may be attributed to the nature of the study population involved. Our study covered the population in the northwest of the island of Ireland, and the findings suggested that only age, CAD, and HF were associated with the increased risk of mortality in the study cohort.

As discussed above, there is no clear consensus regarding the impact of comorbid chronic diseases on the severity and mortality of COVID-19 disease. One possible reason for this disagreement may be the differences in intrinsic factors, such as the genetic characteristics of the population. A large international genomic study of seventeen COVID-19 patient cohorts in nine countries, including Belgium, Brazil, Canada, Germany, Italy, Norway, Spain, Sweden, and the UK, found that rs10490770 risk allele carriers experienced an increased risk of death and severe disease\textsuperscript{25}. It is evident that multiple genetic factors are also associated with a higher risk of death and disease severity in patients with COVID-19, which could explain the lack of consensus between studies on which comorbidities increase the risk of severe disease and death in COVID-19 patients. Therefore, the generalisation of findings may not always be appropriate in COVID-19-related studies.

The study demonstrates notable strengths, particularly in its sample selection. The researchers comprehensively included the entire target population by enrolling all COVID-19 patients admitted to the three acute hospitals in the northwest of the island of Ireland (encompassing both the Republic of Ireland and Northern Ireland) from the onset of the pandemic until May 31, 2021. The geographical coverage of the study sites ensured representation of the entire population within their respective catchment areas, thereby enhancing the robustness of the findings.

However, it is essential to acknowledge certain limitations. Firstly, there were significant missing values in data pertaining to smoking and obesity, which could potentially impact the accuracy and comprehensiveness of the analyses. Additionally, all re-admissions occurring after 48 hours of discharge were treated as separate instances, potentially influencing the total number of cases. Lastly, the study did not incorporate data on cancer, representing a notable gap in understanding the relationship between COVID-19 and this specific comorbidity.
This retrospective analysis of the Northwest of Ireland population hospitalised with COVID-19 was conducted to analyse the impact of existing chronic diseases on the severity and outcomes of COVID-19. The study suggested that age, CAD, and HF had a significant association with increased risk of death in COVID-19 patients. In addition, DM Type-2, COPD, and obesity increase the risk of severe COVID-19 that requires NIV support. Moreover, COPD was found to increase the odds of tracheostomy requirement.

**Conflict of Interests:**
The study is funded by the European Union’s INTERREG VA Programme, managed by the Special EU Programmes Body (SEUPB). No other conflicts of Interest declared.

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**References:**


