What’s the data on diabetes and COVID-19?
China has had 72,134 cases with a fatality rate of 2.3%.

A higher case fatality rate was found in those who were ≥70 yrs and/or had an existing comorbidity. Of this 2.3%, the following has been recorded:

- Cardiovascular disease (10.5%)
- Chronic respiratory disease (6.3%)
- Hypertension (6%)
- Cancer (5.6%)
- Diabetes (7.3%)

In Italy, of the COVID-19-positive deceased, 31.3% had diabetes.

At this time, no data is available on type or duration of diabetes, HbA1c or medication.

The most commonly observed comorbidities in deceased COVID-19-positive patients

<table>
<thead>
<tr>
<th>Diseases</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>249</td>
<td>27.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>213</td>
<td>23.7</td>
</tr>
<tr>
<td>Heart failure</td>
<td>153</td>
<td>17.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>101</td>
<td>11.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>655</td>
<td>73.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>281</td>
<td>31.3</td>
</tr>
<tr>
<td>Dementia</td>
<td>130</td>
<td>14.5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>150</td>
<td>16.7</td>
</tr>
<tr>
<td>Active cancer in the past 5 years</td>
<td>155</td>
<td>17.3</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>37</td>
<td>4.1</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>199</td>
<td>22.2</td>
</tr>
</tbody>
</table>

Number of comorbidities

- 0 comorbidities: 15 (2.1%)
- 1 comorbidity: 151 (21.3%)
- 2 comorbidities: 184 (25.9%)
- 3 comorbidities and over: 360 (50.7%)
<table>
<thead>
<tr>
<th>References</th>
<th>Date</th>
<th>No. of patients</th>
<th>Hospital(s)</th>
<th>Age</th>
<th>Percentage male</th>
<th>Cardiovascular metabolic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertension (%)</td>
<td>Diabetes (%)</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>01.01.20–28.01.20</td>
<td>138</td>
<td>Zhongnan</td>
<td>56 (42–68)</td>
<td>54.3</td>
<td>31.2</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>16.12.19–02.01.20</td>
<td>41</td>
<td>Jinyintan</td>
<td>49 (41–58)</td>
<td>73</td>
<td>15</td>
</tr>
<tr>
<td>Guan et al.</td>
<td>As of 29.01.20</td>
<td>1099</td>
<td>552 in China</td>
<td>47 (35–58)</td>
<td>59.2</td>
<td>14.9</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>01.01.20–28.01.20</td>
<td>99</td>
<td>Jinyintan</td>
<td>55.5 (21–82)</td>
<td>68</td>
<td>–</td>
</tr>
<tr>
<td>Chang et al.</td>
<td>16.01.20-04.02.20</td>
<td>11</td>
<td>3 in Beijing</td>
<td>34 (34–48)</td>
<td>77</td>
<td>–</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>30.12.19–24.01.20</td>
<td>137</td>
<td>9 tertiary in Hubei</td>
<td>57 (20–83)</td>
<td>44.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Meta-analysis for the proportion of hypertension, cardio-cerebrovascular disease and diabetes in COVID-19 cases. Weights are calculated from binary random-effects model analysis. Values represent proportions of the 3 diseases in the COVID-19 patients and 95% CI. Heterogeneity analysis was carried out using Q test, the among studies variation (I² index). Forest plots depict the comparison of the incidences of the 3 diseases in ICU/severe and non-ICU/severe patients.
Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China

Bo Li1 · Jing Yang1,2 · Faming Zhao3 · Lili Zhi4 · Xiqian Wang1 · Lin Liu1 · Zhaohui Bi1 · Yunhe Zhao1

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Abstract
Background Studies have reminded that cardiovascular metabolic comorbidities made patients more susceptible to suffer 2019 novel corona virus (2019-nCoV) disease (COVID-19), and exacerbated the infection. The aim of this analysis is to determine the association of cardiovascular metabolic diseases with the development of COVID-19.

Methods A meta-analysis of eligible studies that summarized the prevalence of cardiovascular metabolic diseases in COVID-19 and compared the incidences of the comorbidities in ICU/severe and non-ICU/severe patients was performed. Embase and PubMed were searched for relevant studies.

Results A total of six studies with 1527 patients were included in this analysis. The proportions of hypertension, cardio-cerebrovascular disease and diabetes in patients with COVID-19 were 17.1%, 16.4% and 9.7%, respectively. The incidences of hypertension, cardio-cerebrovascular diseases and diabetes were about twofolds, threefolds and twofolds, respectively, higher in ICU/severe cases than in their non-ICU/severe counterparts. At least 8.0% patients with COVID-19 suffered the acute cardiac injury. The incidence of acute cardiac injury was about 13 folds higher in ICU/severe patients compared with the non-ICU/severe patients.

Conclusion Patients with previous cardiovascular metabolic diseases may face a greater risk of developing into the severe condition and the comorbidities can also greatly affect the prognosis of the COVID-19. On the other hand, COVID-19 can, in turn, aggravate the damage to the heart.

Keywords COVID-19 · 2019-nCoV · Cardiovascular metabolic diseases · Cardiac injury

Introduction
During the past two decades, the outbreak and prevalence of severe acute respiratory infections have been seen as one of the most serious hazards to global health. Both two prominent coronaviruses, 2002 SARS-CoV and 2012 MERS-CoV, have markedly affected humans, causing 8422 and 1600 infections, as well as 916 and 574 deaths, respectively [1, 2].

In early December 2019, a series of pneumonia cases with unknown reason emerged in Wuhan, Hubei, China. High-throughput sequencing from lower respiratory tract samples has revealed a novel coronavirus that was named 2019 novel coronavirus (2019-nCoV) and also named SARS-CoV-2 [3]. As of February 17th, 2020, 70,636 confirmed cases and 1772 death cases have been documented in China. 2019-nCoV also targets the respiratory tract and shares many similar clinical symptoms with SARS-CoV and MERS-CoV [3]. Common symptoms include fever, fatigue, and dry cough, followed always by anorexia, myalgia, dyspnea, and so on.
Lymphopenia and prolonged prothrombin time are also the most common characteristics [4–6].

In addition, as cardiologists, we are also concerned about whether patients with cardiovascular disease are at greater risk for 2019-nCoV, and whether new coronavirus infections have an impact on the cardiovascular system. Previous studies have shown a relationship between cardiovascular metabolic diseases and SARS and MERS [9–11]. A systematic analysis of 637 MERS-CoV cases showed that diabetes and hypertension are prevalent in about 50% of the patients and cardiac diseases are present in 30% of the cases [11]. Diabetes was seen as an independent predictor for mortality and morbidity in patients with SARS [9]. With the spread of 2019-nCoV and increase of the cases, more and more 2019-nCoV infected individuals exhibit comorbidities such as hypertension, diabetes and cardio-cerebrovascular disease. In Chen’s study of 99 cases, 40% patients had cardio-cerebrovascular disease [6], and in Huang’s study of 41 cases, 20% patients had diabetes [4]. These cardiovascular metabolic comorbidities might render them more susceptible to poor prognosis. Given the rapid spread of 2019-nCoV, an updated meta-analysis with significantly larger sample sizes by integrating the published studies is urgently warranted. Accordingly, the present analysis will not only identify the cardiovascular epidemiological and clinical characteristics of 2019-nCoV infection with greater precision but also unravel the impact of the infection on the cardiac injury.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses of individual participant data (the PRISMA-IPD) statement was followed for the conduct and reporting of this meta-analysis [12].

Data source, search strategy, and inclusion criteria

To identify all the studies illustrating the prevalence and impact of cardiovascular metabolic diseases in 2019 novel coronavirus infection in China, EMBASE and PubMed were carefully searched from December 2019 to February 2020. The following search terms or keywords were used alone or in combination: ‘novel coronavirus’, ‘influenza’, ‘pneumonia’, ‘cardiovascular disease’, ‘hypertension’, ‘diabetes’ and ‘cardiac injury’.

Inclusion criteria are as follows: (1) comparative studies: randomised controlled trials RCTs or non-RCTs published in English; (2) study population: more than ten participants were included in the study; (3) study intervention: patients in the studies should be confirmed to have been infected by 2019 novel coronavirus; (4) parameters: the comorbidities of cardiovascular metabolic diseases and the outcome of cardiac injury should be given. Case reports, non-human studies, studies without adequate information, and studies written in Chinese (for the fear of data duplication) were excluded in the present meta-analysis.

Data extraction and study quality assessment

Prevalence of comorbidities including hypertension, cardiovascular and cerebrovascular diseases and diabetes (Table 1 and Fig. 2) together with clinical outcome of cardiac injury (confirmed by elevation of Troponin I/T, or the creatine kinase seen as the second choice if Troponin I/T were not provided) were extracted from the identified studies (Table 1 and Fig. 3). The primary outcome measure was to compare the prevalence of comorbidities and impact on cardiac injury in ICU and Non-ICU cases (severe and non-severe data as the second choice if ICU data was not provided). Cochrane Collaboration’s tool was followed to assess the risk of bias.

Data synthesis and statistical analysis

All analyses were performed using OpenMeta Analyst version 10.10 (https://www.cebm.brown.edu/open_meta) and RevMan software version 5.3. Forest plots were used to illustrate the prevalence of the cardiovascular metabolic diseases in 2019-nCov infection severity from the selected studies as well as the impact of the 2019-nCov infection on the cardiac injury. The results of the included studies were performed with fixed-effect models (Mantel–Haenszel method) [13] or random-effect models in cases of significant heterogeneity between estimates [14]. We used the I^2 statistic to assess the magnitude of heterogeneity: 25%, 50%, and 75% represented low, moderate, and high degrees of heterogeneity, respectively. The chosen of the proper effect model was based on the analysis results: the fixed effect model was used if I^2 < 50% and the random effect model was used if I^2 ≥ 50% [15].

Results

Selected studies and baseline characteristics

After initially identifying 399 articles, 111 duplicate documents were identified. Of the leaving trials, after review of the titles and abstracts, 277 documents of non-human researches, reviews and studies that were not clinical trials were excluded. The leaving 11 studies were carefully
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and detailed evaluated. At last, six studies were excluded, because the participants of the trials did not meet the criteria we have set. Then one study published in MedRxiv was added. Finally, a total of six studies with 1527 patients were included [4–6, 8, 16, 17] (Fig. 1). All of the selected studies were published in 2020 with different sample patient sizes that ranged from 11 to 1099 patients (Table 1 summarizes the study characteristics).

### Primary outcomes

Systematic analysis of studies that described the epidemiological and clinical features of COVID-19 cases and reported the prevalence of cardiovascular metabolic diseases as well as the impact on cardiac injury in the infectious disease, has identified six reports with 1527 patients (Table 1). The majority of the cases were localized in Wuhan, or recent travel to Wuhan, or contact people from Wuhan. The median ages were, respectively, 56, 49, 47, 55.5, 34 and 57 years old according to the six studies. The infection was diagnosed throughout the whole spectrum of age covering from newborn to 92 years old. In all of the studies, men were more likely to be infected than women and the overall proportion of male is 57.8%.

Meta-analysis for the identified studies showed that the most prevalent cardiovascular metabolic comorbidities were hypertension (17.1%, 95% CI 9.9–24.4%) and cardio-cerebrovascular disease (16.4%, 95% CI 6.6–26.1%), followed by diabetes (9.7%, 95% CI 6.9–12.5%) (Fig. 2). There was a significant heterogeneity (Cochran's $Q$) in the estimates of comorbidities among the identified studies with an $I^2$ index varied from 47 to 95% (Fig. 2).

### Table 1 Number, age, sex and cardiovascular metabolic diseases of patients of the 6 included studies

<table>
<thead>
<tr>
<th>References</th>
<th>Date</th>
<th>Number of patients</th>
<th>Hospital</th>
<th>Age (years)</th>
<th>Sex (male, %)</th>
<th>Cardiovascular metabolic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al. [5]</td>
<td>2020.01.01–2020.01.28</td>
<td>138</td>
<td>Zhongnan Hospital</td>
<td>56 (42–68)</td>
<td>54.3</td>
<td>Hypertension: 31.2, Diabetes: 10.1, Cardiac: 19.6</td>
</tr>
<tr>
<td>Huang et al. [4]</td>
<td>2019.12.16–2020.01.02</td>
<td>41</td>
<td>Jinyintan Hospital</td>
<td>49 (41–58)</td>
<td>73</td>
<td>Hypertension: 15, Diabetes: 20, Cardiac: 15</td>
</tr>
<tr>
<td>Guan et al. [8]</td>
<td>As of 2020.01.29</td>
<td>1099</td>
<td>552 hospitals in China</td>
<td>47 (35–58)</td>
<td>59.2</td>
<td>Hypertension: 14.9, Diabetes: 7.4, Cardiac: 3.9</td>
</tr>
<tr>
<td>Chen et al. [6]</td>
<td>2020.01.01–2020.01.28</td>
<td>99</td>
<td>Jinyintan Hospital</td>
<td>55.5 (21–82)</td>
<td>68</td>
<td>Hypertension: 12, Diabetes: 40, Cardiac: 13*</td>
</tr>
<tr>
<td>Chang et al. [16]</td>
<td>2020.01.16–2020.02.04</td>
<td>11</td>
<td>3 hospitals in Beijing</td>
<td>34 (34–48)</td>
<td>77</td>
<td>Hypertension: –, Diabetes: –, Cardiac: –</td>
</tr>
</tbody>
</table>

*Fig. 1 Flow diagram of the study selection process*
We then compared the difference of the prevalence of the three diseases between severe patients and non-severe patients (or ICU patients vs non-ICU patients according to the data in the studies). For hypertension and cardia-cerebrovascular disease, the heterogeneity test results were calculated as $I^2 = 47\%$ and $26\%$. Thus, the fixed-effect model was used for further analyses. The results from the three included studies (with a total amount of 1278 patients) showed that hypertension accounted for 28.8% of ICU/severe cases, but 14.1% of non-ICU/severe cases. A similar pattern was found in cardia-cerebrovascular disease statistics: it accounted for 16.7% of ICU/severe cases, but 6.2% of non-ICU/severe cases. The proportion hypertension and cardia-cerebrovascular disease were both statistically significant higher in ICU/severe patients compared to the non-ICU/severe patients [hypertension: RR = 2.03, 95% CI (1.54, 2.68), $Z=5.04, P<0.00001$; cardia-cerebrovascular disease: RR = 3.30, 95% CI (2.03, 5.36), $Z=4.81, P<0.00001$] (Fig. 2). For diabetes, the heterogeneity test showed that $I^2 = 67\%$, and so the random effect model was used. Diabetes accounted for 11.7% of ICU/severe cases, but 4.0% of non-ICU/severe cases. The result indicated a higher proportion of diabetes in ICU/severe patients but without statistical significance [RR = 2.21, 95% CI (0.88, 5.57), $Z=1.68, P=0.09$] (Fig. 2).

At last, we focused on the impact of the COVID-19 on the cardiac injury. Two studies that gave clear data were statistically analyzed, and the data showed that 8.0% (95% CI 4.1–12.0%) patients might be suffered from an acute cardiac injury. Another two studies only gave the data of creatine kinase, if it can be seen as a biomarker of cardiac injury, the proportion might be 11.5% (95% CI 7.8–15.2%). When we attempted to compare the differences of cardiac injury incidences between ICU/severe patients and non-ICU/severe patients, we just included the two studies which specifically identified myocardial injury. The data again showed a significant higher incidence of acute cardiac injury in ICU/severe patients compared to the non-ICU/severe patients [RR = 13.48, 95% CI (3.60, 50.47), $Z=3.86, P=0.00001$] (Fig. 3). The funnel plots demonstrated symmetrical distributions of the effect size of hypertension, cardia-cerebrovascular diseases and cardiac injury on either side of the pooled estimate, but a non-symmetrical distribution of the effect size of diabetes (Fig. 4).

**Discussion**

Coronaviruses are enveloped RNA viruses, which include six species that can cause diseases in humans to our knowledge [18]. Four viruses among them (229E, OC43, NL63, and HKU1) have been reported to cause common cold symptoms in immunocompetent individuals [18]. However, the two other strains are the infamous SARS-CoV and MERS-CoV, which have been linked to fatal illness and caused plagues and large numbers of deaths [19]. Complete genome sequences of 2019-nCoV showed that it is identified as a novel betacoronavirus belonging to the sarbecovirus subgenus of Coronaviridae family, the same subgenus with SARS-CoV [3].

According to previous research on SARS-CoV, the presence of comorbidities increased the mortality risk, with cardiac disease and diabetes being the most important components to predict adverse outcomes [20]. Cardiac disease and diabetes increase the risk of death by twice as much as other risk factors [20]. Thus, it is necessary for us to evaluate the prevalence of cardiac and metabolic diseases in COVID-19. The present systematic analysis summarized the data from all of the five studies of COVID-19. The results demonstrated that the overall proportion of hypertension, cardia-cerebrovascular disease and diabetes were, respectively, 17.1%, 16.4% and 9.7%. According to Summary of the 2018 report on cardiovascular diseases in China, the morbidities of the hypertension and diabetes were, respectively, 23.2% and 10.9%, and there were about 13 million of cerebrovascular disease patients and 11 million of cardiovascular patients [21]. Therefore, comparing the data to the report, we did not find that people with hypertension and diabetes were more susceptible to 2019-nCoV infection. The prevalence of hypertension and diabetes in people infected with the virus is about the same as in the general population, even slightly lower. However, comparing the general population, the incidence of cardia-cerebrovascular disease in patients with COVID-19 is obviously much higher.

Due to the sample size and limited time so far, data collection is still incomplete, and most of the studies have not analyzed comorbidities in death cases. So the relationship between cardiovascular metabolic diseases and COVID-19-induced death cannot be determined. But what is assuredly is that patients with hypertension, cardia-cerebrovascular diseases or diabetes are more likely to develop severe/ICU cases after 2019-nCoV infection. The overall proportion of hypertension, cardia-cerebrovascular diseases and diabetes were about twofolds, threefolds and twofolds, respectively, higher in ICU/severe cases than in their non-ICU/severe counterparts. Although the difference of diseases in the meta-analysis is not statistical,
Fig. 3 Meta-analysis for the incidence of cardiac injury in COVID-19 cases. Weights are calculated from binary random-effects model analysis. Values represent proportions of the cardiac injury in the COVID-19 patients and 95% CI. Heterogeneity analysis was carried out using Q test, the among studies variation (I² index). Forest plots depict the comparison of the incidences of cardiac injury in ICU/severe and non-ICU/severe patients.

Fig. 4 Funnel plots of the comparisons of hypertension, cardia-cerebrovascular disease, diabetes and acute cardiac injury between ICU/severe and non-ICU/severe patients.
the RR value is about 2.21, and we consider this might because of the sample size of included studies and the algorithm adopts the random effect model which is a more conservative approach. So we speculate the result might reach statistical significance when more researches publish their data.

Another important finding is the damage the virus did to the heart. According to the present summary, at least 8.0% patients with COVID-19 suffered acute cardiac injury. In Chen’s report, the first death was a 61-year-old man with no previous chronic underlying disease. After he was admitted by ICU, he had developed severe respiratory failure, heart failure, and sepsis, and then experienced a sudden cardiac arrest on the 11th day of admission and was declared dead [6]. This case reminded us that patients with a novel coronavirus might develop acute cardiac injury. And further analysis indicates us that the incidence of myocardial injury is much higher in ICU/severe patients, about 13 folds more than non-ICU/cardiac patients. And furthermore, the observation also reminded us that patients with COVID-19 associated with unstable angina or STEMI have poor cardiac reserve, lower tolerance to severe pneumonia, and are more likely to develop cardiac insufficiency, leading to deterioration. According to the information released by Shanghai health commission, the first COVID-19 death in Shanghai was a patient 88 years old, with a serious history of hypertension, cardiac dysfunction. The analysis of death causes suggested that the patient died of heart failure and systemic multiple organ dysfunction, and in the course of its onset, the 2019 nCoV infection is only the inducement.

The pathogenesis of 2019 nCoV infection-related acute myocardial injury is still unknown. But according to the clinical presentation and lab data of the disease, as well as the pathogenesis of SARS-CoV, It can be speculated that 2019-nCoV infection may affect the cardiovascular system through multiple mechanisms.

First, viral infection directly causes damage to cardiomyocyte. According to Oudit’s study, SARS-CoV viral RNA was detected in 35% of autopsied human heart samples from SARS-CoV infected patients during the Toronto SARS outbreak [22]. And they also confirmed that pulmonary infection with the human SARS-CoV in mice led to an ACE2-dependent myocardial infection [22]. ACE2 is an important target for SARS-CoV [23], and molecular modelling has shown high structural similarity between the receptor-binding domains of SARS-CoV and 2019-nCoV [24]. ACE2 expression is highly tissue-specific, mainly expressed in the cardiovascular, renal and gastrointestinal systems, with a small amount expressed in lung cells. Therefore, in addition to coronaviruses causing pneumonia through ACE2 receptors in lung epithelial cells, we also need to pay attention to possible viral effects on myocardial tissue. Second, hypoxaemia may be also an important reason of cardiac injury. In Huang’s study, 32% COVID-19 patients had various degree of hypoxaemia and need required high-flow nasal cannula or higher-level oxygen support. In Chen’s study, up to 76% of patients require oxygen therapy. Due to severe 2019-nCoV infection, the pneumonia may cause significant gas exchange obstruction, leading to hypoxaemia, which significantly reduces the energy supply by cell metabolism, and increases anaerobic fermentation, causing intracellular acidosis and oxygen free radicals to destroy the phospholipid layer of cell membrane. Meanwhile, hypoxia-induced influx of calcium ions also leads to injury and apoptosis of cardiomyocytes. Third, Huang’s study noted that high concentration of IL-1β, IFN-γ, IP-10 and MCP-1 could be detected in patients infected with 2019-nCoV, which might lead to activated T-helper-1 (Th1) cell responses [4]. Furthermore, they also found that ICU patients had much higher concentrations of inflammatory factors than those non-ICU patients, suggesting that the cytokine storm was associated with disease severity [4]. In addition, repeated floods of catecholamines due to anxiety and the side effects of medication can also lead to myocardial damage.

In conclusion, patients with previous cardiovascular metabolic diseases may face a greater risk of infection of 2019-nCoV and it can also greatly affect the development and prognosis of pneumonia. Simultaneously, we should pay close attention to viral infection-related heart damage in the course of disease treatment.

Funding This study was supported by the Natural Science Foundation of China (no. 81700321), the Key Research and Development Plan of Shandong Province (2018GSF118140).

Compliance with ethical standards
Conflict of interest None declared.

References


Characteristics of COVID-19 patients dying in Italy
Report based on available data on March 30\textsuperscript{th}, 2020

1. Sample

The present report describes characteristics of 10,026 COVID-19 patients dying in Italy.* Geographic distribution across the 19 regions and 2 autonomous provinces of Trento and Bozen is presented in the table below. Data are update to March 30\textsuperscript{th}, 2020.

\begin{table}[h]
\begin{tabular}{lll}
\hline
REGIONS & N & \% \\
\hline
Lombardia & 6,366 & 63.5 \\
Emilia-Romagna & 1,432 & 14.3 \\
Piemonte & 574 & 5.7 \\
Veneto & 431 & 4.3 \\
Liguria & 271 & 2.7 \\
Trento & 129 & 1.3 \\
Marche & 127 & 1.3 \\
Lazio & 124 & 1.2 \\
Toscana & 116 & 1.2 \\
Puglia & 92 & 0.9 \\
Friuli-Venezia Giulia & 89 & 0.9 \\
Campania & 60 & 0.6 \\
Bolzano & 58 & 0.6 \\
Sicilia & 32 & 0.3 \\
Valle d'Aosta & 26 & 0.3 \\
Umbria & 25 & 0.2 \\
Abruzzo & 23 & 0.2 \\
Sardegna & 20 & 0.2 \\
Calabria & 18 & 0.2 \\
Molise & 9 & 0.1 \\
Basilicata & 4 & 0.0 \\
\hline
Total & 10,026 & 100.0 \\
\end{tabular}
\end{table}

* COVID-19 related deaths presented in this report are those occurring in patients who test positive for SARS-CoV-2 RT by PCR, independently from pre-existing diseases.
2. Demographics

Mean age of patients dying for COVID-2019 infection was 78 (median 79, range 26-100, IQR 73 -85). Women were 3,088 (30.8%). Figure 1 shows that median age of patients dying for COVID-2019 infection was more than 15 years higher as compared with the national sample diagnosed with COVID-2019 infection (median age 62 years). Figure 2 shows the absolute number of deaths by age group. Women dying for COVID-2019 infection had an older age than men (median age women 82 - median age men 78).

Figure 1. Median age of patients with COVID-2019 infection and COVID-19 positive deceased patients

![Median age of patients with COVID-2019 infection and COVID-19 positive deceased patients](image1)

Figure 2. Absolute number of deaths by age group

![Absolute number of deaths by age group](image2)

Note: For 2 deceased persons age was not possible to be evaluated
3. Pre-existing conditions

Table 1 presents most common comorbidities diagnosed before COVID-19 infection. Data on diseases were based on chart review and was available on 909 patients dying in-hospital for whom it was possible to analyse clinic charts. Mean number of diseases was 2.7 (median 3, SD 1.6). Overall, 2.1% of the sample presented with no comorbidities, 21.6% with a single comorbidity, 24.5% with 2, and 51.7% with 3 or more.

Before hospitalization, 28% of COVID-19 positive deceased patients followed ACE-inhibitor therapy and 16% angiotensin receptor blockers-ARBs therapy. This information can be underestimated because data on drug treatment before admission were not always described in the chart.

### Table 1. Most common comorbidities observed in COVID-19 positive deceased patients

<table>
<thead>
<tr>
<th>Diseases</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>249</td>
<td>27.4</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>209</td>
<td>23.0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>149</td>
<td>16.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>109</td>
<td>12.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>668</td>
<td>73.5</td>
</tr>
<tr>
<td>Diabetes</td>
<td>286</td>
<td>31.5</td>
</tr>
<tr>
<td>Dementia</td>
<td>146</td>
<td>16.1</td>
</tr>
<tr>
<td>COPD</td>
<td>166</td>
<td>18.3</td>
</tr>
<tr>
<td>Active cancer in the past 5 years</td>
<td>150</td>
<td>16.5</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>42</td>
<td>4.6</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>216</td>
<td>23.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of comorbidities</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 comorbidities</td>
<td>19</td>
<td>2.1</td>
</tr>
<tr>
<td>1 comorbidity</td>
<td>197</td>
<td>21.6</td>
</tr>
<tr>
<td>2 comorbidities</td>
<td>223</td>
<td>24.5</td>
</tr>
<tr>
<td>3 comorbidities and over</td>
<td>470</td>
<td>51.7</td>
</tr>
</tbody>
</table>

4. Diagnosis of hospitalization

In 94.9% of hospitalizations, conditions (e.g. pneumonia, respiratory failure) or symptoms (e.g. fever, dyspnoea, cough) compatible with COVID-19 were mentioned. In 46 cases (5.1% of cases) the diagnosis of hospitalization was not related to the infection. In 7 cases the diagnosis of hospitalization concerned exclusively neoplastic pathologies, in 18 cases cardiovascular pathologies (for example IMA, heart failure, stroke), in 11 cases gastrointestinal pathologies (for example cholecystitis, perforation of the intestine, intestinal obstruction, cirrhosis), in 10 cases other pathologies.
5. **Symptoms**

*Figure 3* shows symptoms most commonly observed at hospital admission. Fever, dyspnoea and cough were the most commonly observed symptoms, while diarrhoea and haemoptysis were less commonly observed. Overall, 6.0% of patients did not present any symptoms at hospital admission.

*Figure 3. Most common symptoms observed in COVID-19 positive deceased patients*

6. **Acute conditions**

Acute Respiratory Distress syndrome was observed in the majority of patients (96.5% of cases), followed by acute renal failure (25.7%). Acute cardiac injury was observed in 11.6% and Superinfection in 11.2% of cases.

7. **Treatments**

Antibiotics were used by 86% of patients during hospital stay, while less used were antivirals (54%) and corticosteroids (34%). Concomitant use of these 3 treatments was observed in 19.3% of cases.

Out of COVID-19 positive deceased patients, 1.7% were treated with Tocilizumab during hospitalization.
8. **Time-line**

Figure 4 shows, for COVID-19 positive deceased patients, the median times, in days, from the onset of symptoms to death (9 days), from the onset of symptoms to hospitalization (4 days) and from hospitalization to death (5 days). The time from hospitalization to death was 2 days longer in those who were transferred to intensive care than those who were not transferred (6 days vs. 4 days).

**Figure 4.** Median hospitalization times (in days) in COVID-19 positive deceased patients

<table>
<thead>
<tr>
<th>Hospitalization Event</th>
<th>Median Number of Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms --&gt; Death</td>
<td>9</td>
</tr>
<tr>
<td>Onset of symptoms --&gt; Hospitalization</td>
<td>4</td>
</tr>
<tr>
<td>Hospitalization --&gt; Death</td>
<td>5</td>
</tr>
<tr>
<td>Hospitalization --&gt; Death (NO ICU)</td>
<td>4</td>
</tr>
<tr>
<td>Hospitalization --&gt; Death (YES ICU)</td>
<td>6</td>
</tr>
</tbody>
</table>

9. **Deaths under the age of 50 years**

As of March 30th, 112 out of the 10,026 (1.1%) positive COVID-19 patients under the age of 50 died. In particular, 23 of these were less than 40 years, 19 men and 4 women (age range between 26 and 39 years). For 2 patients under the age of 40 years no clinical information is available; the remaining 15 had serious pre-existing pathologies (cardiovascular, renal, psychiatric pathologies, diabetes, obesity) and 6 had no major pathologies.

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This report was produced by COVID-19 Surveillance Group

**Members of the COVID-19 Surveillance Group**

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Managing diabetes during intercurrent illness in the community

February 2013
Rationale and remit
This document has been developed to provide information and guidance on the community management of diabetes in adults during episodes of illness. It is intended to serve as a helpful resource for a range of groups, including medical professionals (e.g. nurses, GPs) and non-medical professionals (e.g. those working in residential care, prisons, young offender institutes or mental health units).

The recommendations have been developed by Training, Research and Education for Nurses in Diabetes (TREND-UK); the authors are listed below. Other diabetes organisations have been involved in the development of the guidance via a process of review, and are listed below as the document reference group. The document has also been reviewed and endorsed by NHS Diabetes.

When implementing any advice in the document, full account should be taken of the local context and any action taken should be in line with statutory obligations required of the organisation and individual. No part of the publication should be interpreted in a way that would knowingly put anybody at risk.

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Introduction: The challenge of diabetes and intercurrent illness

Although people with diabetes do not necessarily become ill more often than anybody else, if their diabetes is inadequately controlled they may be more prone to certain infections (American Diabetes Association, 1998). They may also respond differently to illness according to the type of diabetes they have and the illness they are experiencing.

However, when a person with diabetes is unwell, it is likely that their blood glucose levels will rise (this is known as hyperglycaemia; Fowler, 2009). The signs and symptoms of hyperglycaemia (which may occur even if the person is not eating) include (NHS Choices, 2012):
- Increased thirst.
- Dry mouth.
- Passing more urine than usual.
- Tiredness or lethargy.
- High glucose levels in the urine or blood.

Examples of illnesses that may cause hyperglycaemia include:
- The common cold.
- Influenza.
- Stomach upset.
- Urinary infection.
- Chest infection.
- Abscesses.
- Injury, such as a broken bone.

If someone does not know how to manage their diabetes during periods of illness, other problems may arise, such as dehydration or the development of certain serious acute diabetes conditions. The correct advice can prevent this happening.

Potential acute diabetes conditions which occur when a person with diabetes is unwell

In some circumstances during illness, the serious conditions of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state (HHS) can develop.

**Diabetic ketoacidosis**

DKA is a condition that requires urgent hospital treatment. It occurs when there is not enough glucose entering the cells for energy owing to insufficient insulin being available. As a result, the body begins to use fat stores as an alternative source of energy, which results in acidic ketones being produced. These disrupt the normal functioning of the body’s processes. This may be more likely during intercurrent illness. Although most cases of DKA occur in people with type 1 diabetes, it can develop in people with type 2 diabetes during times of severe illness (Diabetes UK, 2012a).

The signs and symptoms of DKA include (Hansen and Møller, 2010):
- Excessive thirst.
- Passing frequent large volumes of urine.
- Dehydration.
- Shortness of breath and laboured breathing.
- Abdominal pain, leg cramps.
- Nausea and vomiting.
- Mental confusion and drowsiness.
- Ketones (which smell like pear drops) can be detected on the person’s breath or in the blood or urine.

If left untreated, DKA can lead to coma and even death.

**Hyperosmolar hyperglycaemic state**

HHS is a potentially life-threatening emergency, which requires hospital treatment. It occurs in people with type 2 diabetes, particularly the elderly, who develop very high blood glucose levels (often over 40 mmol/L) over a period of several days or weeks. It leads to severe dehydration, confusion and coma if not identified and treated correctly.

The signs and symptoms of HHS include (Stoner, 2005):
- Disorientation or confusion.
- Passing frequent large amounts of urine.
- Thirst and dry mouth.
- Nausea.

In the later stages of HHS the person becomes drowsy and gradually loses consciousness.

General principles of managing diabetes during intercurrent illness

**Aims**

When managing a person with diabetes during intercurrent illness the aims are to:
- Continue to manage the person’s diabetes and blood glucose levels.
- Ensure the person receives sufficient calorie intake and address dehydration with fluid replacement.
- Test for and manage any ketones present in the body.
- Recognise whether the person requires additional medical attention.
Management of a person’s diabetes and blood glucose levels

When a bacterial or viral infection (such as a common cold) is present, blood glucose levels may rise in response, even if no food is eaten. For this reason, during times of illness, people with diabetes who have access to blood glucose monitoring should monitor and record their blood glucose levels at least four times a day (that is, at mealtimes – even if they are not eating – and at bedtime). Those who do not have access to blood glucose monitoring should be mindful of the symptoms of hyperglycaemia.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>General recommendations for carers and healthcare professionals based on the authors’ experience</th>
<th>Relevant advice from drug Summaries of Product Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>General advice for all people with diabetes</td>
<td>Blood glucose levels should be tested if a meter is available. If it is not available, be mindful of the symptoms of hyperglycaemia.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>The person should continue to take their medication while the blood glucose level is normal or high unless they are feeling severely unwell (e.g. vomiting, diarrhoea or fever) or are dehydrated, in which case, metformin should be temporarily stopped. The dose should be restarted once the person is feeling better. Metformin should also be stopped in individuals where the severity of their illness requires hospitalisation or confinement to bed.</td>
<td>Contraindicated in people with DKA and in those with acute conditions with the potential to alter renal function such as dehydration and severe infection (Merck Serono, 2010).</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors (acarbose)</td>
<td>The person should continue to take their medication while the blood glucose level is normal or high. Acarbose should not be used in people who are vomiting or experiencing severe diarrhoea. It should also not be used in cases of inflammatory bowel disease or DKA.</td>
<td>No relevant information identified in the Summary of Product Characteristics.</td>
</tr>
<tr>
<td>Sulphonylureas (glibenclamide, glimepiride, glipizide, tolbutamide)</td>
<td>The person should continue to take their medication while the blood glucose level is normal or high. If they are unable to eat or drink, they may be at risk of hypoglycaemia (low blood glucose levels) and the medication may need to be reduced or stopped temporarily.</td>
<td>Contraindicated in people with DKA (Accord Healthcare Ltd, 2012; Actavis UK Ltd, 2011; Pfizer Ltd, 2012; Servier Laboratories Ltd, 2012; Zentiva, 2012).</td>
</tr>
<tr>
<td>Meglitinides (nateglinide, repaglinide)</td>
<td>The person should continue to take their medication while the blood glucose level is normal or high. If they are unable to eat or drink, they may be at risk of hypoglycaemia (low blood glucose levels) and the medication may need to be reduced or stopped temporarily.</td>
<td>Contraindicated in people with DKA (Novartis Pharmaceuticals UK Ltd, 2011; Novo Nordisk Ltd, 2012).</td>
</tr>
<tr>
<td>Thiazolidinediones (pioglitazone)</td>
<td>The person should continue to take their medication while the blood glucose level is normal or high. Medical advice should be sought if the person experiences unusual shortness of breath or localised swelling as this may be a sign of possible heart failure, particularly in the elderly.</td>
<td>Contraindicated in people with DKA and can cause fluid retention and oedema (Takeda UK Ltd, 2013).</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin)</td>
<td>The person should continue to take their medication while the blood glucose level is normal or high. Medical advice should be sought if the person is vomiting, dehydrated or experiencing severe abdominal pain. Severe abdominal pain may indicate pancreatitis.</td>
<td>Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe. abdominal pain. If pancreatitis is suspected, potentially suspect medicinal products should be discontinued (Boehringer Ingelheim Ltd, 2012; Bristol Myers Squibb-AstraZeneca, 2012a; Merck Sharp &amp; Dohme Limited, 2013; Novartis Pharmaceuticals UK Ltd, 2013).</td>
</tr>
</tbody>
</table>
People with type 2 diabetes who do not manage their diabetes with insulin should generally continue to take their medication as usual. Manufacturer’s guidance and specific advice based on the experience of the authoring panel is provided in Table 1.

If a person is taking insulin and his or her blood glucose levels are higher than usual, the insulin dose may need to be increased (see Figure 1). If their blood glucose levels are lower than usual, the insulin dose may need to be reduced. Ensure sufficient calorie intake and address dehydration

If the individual is unwell and unable to eat their usual meals, it is important that they continue to eat or drink some carbohydrate (starchy or sugary foods) as a source of energy. Table 2 provides a list of food alternatives that can be used. As a rough guide, the person should try to take two to three servings from the list provided approximately four to five times a day. They should also be encouraged to drink at least 4 to 6 pints (2.5 to 3.5 L) of sugar-free fluid in 24 hours (at least 100 mL each hour) in order to avoid dehydration.

However, if the individual starts vomiting or is unable to keep fluids down, urgent medical advice should be immediately sought.

Testing and management of ketones
During illness a simple blood or urine test can be used to show if the body is producing ketones. People with type 1 diabetes should always test for ketones if they feel unwell and their blood glucose is more than 13 mmol/L. People with type 2 diabetes do not usually test for ketones. However, healthcare professionals should test for ketones in anyone with type 1 or type 2 diabetes who is acutely unwell and vomiting. Figure 1 provides advice on how to interpret the ketone test result in those who are taking insulin.

Treatment of special groups of people with diabetes
Table 3 provides an overview of specific advice regarding intercurrent illness for particular groups of people with diabetes. It is important that advice about what to do when feeling unwell is reinforced regularly by a healthcare professional so that the person with diabetes knows what to do when the situation arises.

Conclusions
Intercurrent illness in people with diabetes should be taken seriously because it may increase the risk of hyperglycaemia and other diabetes complications.
It is important that people with diabetes are regularly reminded of what to do when they feel unwell in order that they know what to do if blood glucose levels rise. Such precautions may prevent the development of serious hyperglycaemia, DKA and HHS.


Table 2. Food alternatives (University Hospitals of Leicester NHS Trust, 2009).

<table>
<thead>
<tr>
<th>Type of food alternative</th>
<th>Amount*</th>
<th>Amount*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucozade™ Energy</td>
<td>50 mL</td>
<td>2 fl oz</td>
</tr>
<tr>
<td>Fruit juice†</td>
<td>100 mL</td>
<td>4 fl oz</td>
</tr>
<tr>
<td>Cola (NOT diet)†</td>
<td>100 mL</td>
<td>4 fl oz</td>
</tr>
<tr>
<td>Lemonade (NOT diet)†</td>
<td>150–200 mL</td>
<td>5–7 fl oz</td>
</tr>
<tr>
<td>Milk</td>
<td>200 mL</td>
<td>7 fl oz</td>
</tr>
<tr>
<td>Soup†</td>
<td>200 mL</td>
<td>7 fl oz</td>
</tr>
<tr>
<td>Ice cream†</td>
<td>50 g</td>
<td>2 oz</td>
</tr>
<tr>
<td>Complan®</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Drinking chocolate†</td>
<td>–</td>
<td>3 level tsp (as a drink)</td>
</tr>
<tr>
<td>Ovaltine® or Horlicks®*</td>
<td>–</td>
<td>1 large scoop</td>
</tr>
</tbody>
</table>

*Each serving provides approximately 10 g of carbohydrate.
†Sugar quantities may vary widely according to brand.


Novo Nordisk Ltd (2012) Prandin 0.5 mg, 1 mg, 2 mg Tablets – SPC. Available at: http://bit.ly/U9HCAk (accessed 05.02.2013)


<table>
<thead>
<tr>
<th>Group of people</th>
<th>General recommendations based on the authors’ experience</th>
<th>Relevant advice for healthcare professionals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>It is vital that pregnant women with diabetes who feel unwell seek specialist medical advice immediately. These patients will be under joint obstetric and specialist diabetes care and therefore will have an emergency contact telephone number. Do not be falsely assured by normal or mildly elevated blood glucose levels.</td>
<td>Please refer to NICE (2008) Diabetes in pregnancy: Management of diabetes and its complications from pre-conception to the postnatal period. Clinical Guideline 63. Available at: <a href="http://www.guidance.nice.org.uk/cg63">http://www.guidance.nice.org.uk/cg63</a></td>
</tr>
<tr>
<td>End of life care</td>
<td>The aim of end of life care for people with diabetes is to ensure that, as far as possible, they remain symptom free. Any care given should reduce symptoms and ideally improve the person’s experience of their final days, along with avoiding thirst, dehydration, and diabetes emergencies.</td>
<td>Please refer to Diabetes UK (2012b) End of life diabetes care – Clinical care recommendations. Available at: <a href="http://www.diabetes.org.uk/About_us/Our_Views/Position_statements/End-of-Life-Care/">http://www.diabetes.org.uk/About_us/Our_Views/Position_statements/End-of-Life-Care/</a></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>People with diabetes and chronic kidney disease (CKD; stages 4 or 5) should seek specialist advice if they feel unwell. People with diabetes and CKD who are taking a sulphonylurea (e.g. glimepiride, glitazide) or insulin are more prone to low blood glucose levels (hypoglycaemia) than those without CKD due to the kidney’s inability to excrete insulin efficiently.</td>
<td>The authors were not able to identify any published guidelines relating to illness in those with diabetes and CKD.</td>
</tr>
</tbody>
</table>
| Insulin pumps                          | Insulin pump users can rapidly develop diabetic ketoacidosis (DKA) if their insulin pump fails. If a person’s blood glucose level rises rapidly they should:  
  - Monitor for blood or urine ketones.  
  - Check the pump to ensure that it is working properly.  
  - Check to see if the pump tubing is blocked or disconnected.  
  - Check that the cannula is in the correct place and is secure.  
  All pump users should be advised to carry an insulin pen device with them containing quick-acting insulin that is in date for use in emergencies. Insulin pump users will be under specialist diabetes care and will have an emergency contact telephone number to use should any issues arise. | Please refer to Clinical Knowledge Summaries (2012) Insulin therapy in type 1 diabetes – Management. Scenario: Periods of illness. Available at: http://www.cks.nhs.uk/insulin_therapy_in_type_1_diabetes/management/scenario_periods_of_illness/view_full_scenario                                                                          |
| People with diabetes in residential care| The symptoms of DKA in people with diabetes who live in care and nursing homes can be easily confused with hyper- or hypoglycaemia. Staff may not be skilled in the area of diabetes and may not recognise the symptoms. If there are any concerns about a patient becoming unwell while taking insulin, specialist medical advice should be sought immediately. | Please refer to Diabetes UK (2010) Good clinical practice guidelines for care home residents with diabetes. Available at: http://www.diabetes.org.uk/Documents/About%20Us/Our%20views/Care%20recs/Care-homes-0110.pdf                                                                                     |
| People with diabetes in prisons or young offender institutions | People working in prisons or young offender institutions need to know how to recognise the signs and symptoms of DKA and hyperosmolar hyperglycaemic state (HHS) in people with diabetes, and seek medical help as soon as possible. | Please refer to American Diabetes Association (2008) Diabetes management in correctional institutions. Diabetes Care 31 (Supplement 1): s87–93                                                                 |
| People taking other medications        | Steroids prescribed during intercurrent illness may be associated with worsening hyperglycaemia. Immediate medical advice must be sought from the person prescribing the additional medication. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should also be stopped in those needing to be admitted or confined to bed to lessen the risk of acute kidney injury. | Please refer to the specific Summary of Product Characteristics for further information.                                                                                                                                                                                  |