Deaths for Hospital Acquired Infections in Intensive Care Units and COVID Departments in Italy That May Be Biased for Coronavirus Caused Mortality. Warning for Science and Politics and Further Suggestions

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Short Report

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Abstract

Background Hospital acquired infections (HAIs) are a serious concern for COVID-19 pandemic and its emergency in hospitals and healthcare units in Italy. The incidence of nosocomial infections in the clinical outcomes of COVID-19 is a quite dismissed feature in the crowded debate about how addressing and managing COVID-19 outbreak in Italy.

Methods Statistical methods using Kaplan-Meier plots, Bayesian calculation on RR and Or, regression calculation and confounder ANCOVA tests were applied on publicly data from the Italian Ministry of Health to highlight the rate of HAIs on COVID diagnosis.

Results RR value to die in hospitals during COVID-19 pandemic because of nosocomial infections in 2020, taking into account the number of deaths provided by the Italian Ministry of Health on December 31st 2020 and values about HAIs in current literature, leads to RR = 8.47 (CI_{95} = 8.38-8.56, odds ratio (OR) = 8.55). Hospitalized people have more probability to be healed (median, Me = 35.92) respect to non hospitalized ones (Me = 30.28), whereas hospitalization increased the median of deaths (Me = 29.37) respect to non hospitalized people (Me =24.26).

Conclusions Nosocomial infections may exert a major role, as a confounder, in increasing the dramatic amount of deceases so far accounted to exclusively SARS-CoV2 infections. If such, politics should be much more aware of this concern.

Introduction

Hospital acquired infections (HAIs) still represent a huge concern for intensive care units (ICUs), particularly during COVID-19 emergency, where stressful circumstances may increase the impact of ICU managing on HAI incidence. Malacarne and colleagues, in a multicenter study on 125 different hospitals and healthcare units in Italy carried on 34,472 patients, reported that HAI incidence was 12.6%, with 29.4% in subjects hospitalized in ICUs and 38.7% deaths. Moreover, about 3,148 patients contracted at least one infection during hospitalization in ICU (prevalence 9.1%), with a mortality rate of 35.1% [1]. Elderly subjects, who are the weakest and most critical patients during COVID-19 hospitalization, are particularly frail and more likely to develop HAI (prevalence = 16.1%) respect to younger subjects [2]. The Italian Institute of Statistics reported that a rapid increase in HAI-caused deaths for each year occurred from 2003 (18,668) to 2016 (49,301), whereas the number of total deaths increased from a mean of 587,487 in the period 2015–2019 to 668.443 in 2020 (see: https://www.istat.it/it/archivio/241428). The number of deaths increased of about 13.78%, a value particularly close to the aforementioned incidences in HAIs and accounting for a theoretical number of 80,956 deaths in 2020, particularly next to the value 74,159 reported by the Italian Ministry of Health on December 31st 2020 as a cause of SARS-CoV2 infection.

A recent paper by Giacobbe et al., showed a Kaplan-Meyer plot from a multicenter study with Italian hospitals, where deaths purported to be caused by HAIs, i.e. ventilator associated pneumonia (VAP)

respect to the ones caused by COVID-19, did not exhibit any significant difference (p = 0.4) [3]. In addition, a paper by Carter et al., reported that in older adults the risk of mortality was much more frequently associated with infections from community, rather than from hospital [4]. Establishing how much HAIs affects the impact of COVID-19-dependent mortality in hospitals and healthcare units is particularly crucial. However, the incidence of HAIs is particularly burdensome if associated with the increase in bacterial infections due to the daily use of incorrect habits, such as using poorly renewed face masks [5]. People crowding an emergency unit, as well as other healthcare services, with contaminated face masks, are endowed to both widespread bacteria in the indoor environment and to gather a flowering bacterial microbiota in their nose-mouth systems, particularly before undergoing a catheter or a ventilator device. A paper from Lanini e al., estimated an overall frequency of HAIs of about 6.7% by investigating 9,609 patients, of which 35.8% accounting for lower respiratory tract infections [6]. The possibility that SARS-CoV2 may act as an ignition of bacteria-driven inflammation in these districts, may be particularly significant [7].

Novel strategies addressed to improving hygiene and sanitization conditions in ICUs, such as ozone, are particularly crucial in dampening COVID-19 caused deaths in hospitals, particularly because bacteria are much more widespread in ICUs than SARS-CoV2 [8–10]. The logical consequence of this evidence leads people wondering whether diagnosed COVID-19 deaths, cumulating the gruesome list of daily deceases, are really altogether caused by solely SARS-CoV2 infection or pneumonia coming from HAIs has a leading or significant role in these deaths.

This paper tries to elucidate this awkward issue.

Insights On The Covid-19 Deaths In Italy

By accounting on data coming from the Government institutions for public health, a time series forecast evaluation of deaths in Italy caused only by HAIs, should give, in non emergency period, a number of about 2,356 deaths any year, leading to an estimation for 2020 of about 58,725 deceases, very close to the 74,159 deaths reported by the Italian Ministry of Health on December 31st 2020. It is conceivable that in emergency times, where hospitals are much more crowded of sick patients and healthcare workers, this evaluation may result greatly exacerbated. Zotti et al., evaluated an averaged prevalence of HAI of about 7.84% but estimating a wider range of 0-47.8% of HAI incidence, depending on the different healthcare units and hospital involved in the survey [11]. The Italian Institute of Statistics reported that deaths in Italy amounted to 630000 (page 4 of 10 to the link https://www.istat.it/it/files/2019/07/Statistica-report-Bilancio-demografico-2018.pdf) in 2018, so a number of about 49,000 deaths caused by HAI represents a 7.74%, very close to the HAI values reported so far. So, how many patients really die in ICUs during the current COVID-19 pandemic because of HAIs?

This amount is particularly hard to be correctly estimated, particularly because of frailty due to elderly people with co-morbidities and for season effects [12]. The SPIN-UTI survey reported a mortality rate due to HAI not so far from 17–18%, i.e. on a mean of 2564 patients in 35 ICUs in the year range 2006–2011,

averaged deaths in ICUs due to HAIs amounted to 463, for an age range of 65–66 years [13]. Moreover, Agodi et al., reported that the Relative Risk to die in an ICU due to HAIs increased throughout the years, i.e. RR = 2.25 (CI_{95} = 1.90–2.66) in 2006–2007, RR = 2.96 (CI_{95} = 2.48–3.54 in 2008–2009 and RR = 3.19 (CI_{95} = 2.71–3.74 in 2020-2011[13]. During the first months of the COVID-19 outbreak in Italy, the overall case-fatality was higher (7.2%) than in China (2.3%), despite the fact that when data were stratified for age groups, the re-calculated case-fatality rate was perfectly comparable between Italy and China for ages 0–69, yet rates were higher for Italy in ages ≥ 70 years old, particularly for ages higher than 80. The authors were unable to explain this difference [14].

A recalculation made in our labs of the RR value to die in hospitals during COVID-19 pandemic because of nosocomial infections in 2020, taking into account the number of deaths provided by the Italian Ministry of Health on December 31st 2020 and values about HAIs in current literature, leads to RR = 8.47 (CI_{95} = 8.38–8.56, odds ratio (OR) = 8.55). A correct strategy in public health management should take into account, therefore, regarding the real impact of HAIs in ICUs and health care units during this dramatic COVID-19 emergency. Yet, this concern may have been particularly underestimated during the most acute increase in SARS-CoV2 infections, if politics attempted solutions for patients' hospitalization in ICUs taking into account hotels and further temporary structures such as camp tents, though equipped, but notoriously devoid of stringent measures of HAI dampening respect to an hospital care unit. Furthermore, public mainstream opinion, via either press release or social networks, never moved an outcry or expanded a debate of impact about this concern, probably because any consideration was abruptedly overwhelmed by the dramatic tale about COVID-19 infections and associated deaths we were compelled to hear day by day. Science should wonder if exacerbation following SARS-CoV2 infection was mostly due to super-infections with environmental bacteria, a circumstance that, if it could be true that deaths are closely associated to COVID-19 diagnosis, such deaths might be greatly prevented by reducing HAIs incidence. The close superimposition one can evaluate between estimated HAI-caused deaths and COVID-19 deceases, should suggest for the existence of statistical confounders in the description of COVID-19 pandemic in Italy.

Are There Major Confounders In The Official Count Of Covid-19 Deaths In Italy?

Figure 1A shows the Kaplan-Meier plot of estimated deaths for HAIs (blue plot) and for COVID-19 (red plot) taking into account data from the Italian Ministry of Health from March 8th 2020 to June 8th 2020, showing that differences between the separate ethiopathogenetic conditions in survival percentages were not significant ($p = 0.61$, $z = 0.51$) and suggesting that HAI prevalence in COVID-19 emergency may be quite perfectly hidden as a confounder in the evaluation of coronavirus caused deaths. In an attempt to evaluate if a difference, estimated as linear regression, could be observed by relating the number of subjects undergoing hospitalization respect to the ones assisted in their homes, regression was highly significant (Fig. 1B, $p < 0.0001$), with $R^2 = 0.912$, CI_{95} = 0.864–0.943, in the first month of lockdown in Italy (March 8th 2020-April 8th 2020). This regression was also significant, though in a much lesser extent, for

the association deaths/discharged people (Fig. 1C), for the same lockdown period ($p = 0.031$, $R^2 = 0.991$, $CI_{95} = 0.983–0.995$). A measurement of error in covariates, to identify epidemiological confounders, was therefore applied [15]. Two clusters of data were considered: a) Group A, collecting good outcomes (healing, positive swabs turned to negative, discharged cases) in hospitalized (A1) and non hospitalized (A2) subjects; b) Group B, collecting bad outcomes (deaths) in hospitalized (B1) and non hospitalized (B2) people. Group A covariates in the period March 8th 2020-April 8th 2020, gave a correlation of 0.8308 with $p = 0.007$, (covariance = 88.90, expected values A1 = 41.92 and A2 = 31.28), whereas for group B correlation was − 0.0053, with $p = 0.00772$. (covariance = 31.59, expected values B1 = 31.59 and B2 = 23.42). Covariates evaluation suggests that in the group B confounders may be present, thereby affecting the count of deaths in a high emergency period such as the lockdown. Hospitalized people have more probability to be healed (median, Me = 35.92) respect to non hospitalized ones (Me = 30.28), whereas hospitalization increased the median of deaths (Me = 29.37) respect to non hospitalized people (Me = 24.26). Considering that SARS-CoV2 should have the same covariates in the same population with homogeneously distributed ages and sexes, despite the healthcare place where a patient is treated, a confounding component may affect the distribution of outcomes within the same population.

The incidence of HAIs in this evaluation may be a possible explanation, obviously to be further verified.

Particularly for ICUs, where frailty is much frequent in exposed patients to HAIs, the confounding effect of HAI-caused exacerbations in COVID-19 positive subjects, possibly leading to the worst outcome (death), can be particularly relevant. Bentivegna et al., reported in 2020 a significantly higher incidence in multi-drug resistant bacteria infections in COVID-19 units respect to others (29% vs 19%, $p < 0.05$) [16]. Gathering data and evidence about this huge concern should move politics to revise its perspective about COVID-19 emergency.

How To Address This Concern. Some Suggestion

A thorough hygiene processing able to dampen bacterial contamination in critical units where patients with COVID-19 are hospitalized is particularly urgent and mandatory. In our experience, the use of ozone resulted very promising in addressing this concern, even in treating patients directly [17–19]. Stümpfle and colleagues, at the 30th International Symposium on Intensive Care and Emergency Medicine, reported that ozone fumigation is able to completely eradicate multi-drug resistant bacteria, such as *Acinetobacter baumanii*, in intensive care units [20]. Coronel et al., performed a 16-month prospective study, to evaluate the use of ozone in sanitization, on an on-site treatment of medical wastes considering 10-bed ICUs. Ozone succeeded in reducing bacteria and fungi of a 10^5 factor, dampening to negligible values (quite zero) the previous impact of about $10^{5.86}$ (range $10^{2.35}$-$10^{8.05}$) of bacteria in waste gloves [21]. While ozone was even tested in the past for microbial decontamination in space station environments [22], is use in critical care is quite dismissed, widely replaced by detergents and chemical disinfectants. Microbial agents able to exacerbate the clinical impact of COVID-19, particularly Gram negative bacteria, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* or even *Escherichia coli*, are particularly widespread in hospital *indoor* areas. Hofmaenner and colleagues, reported that many Gram

negative bacteria are much more present in sinks and siphons of ICUs than SARS-CoV2 [9]. Ozone is completely enabled to kill *Pseudomonas aeruginosa* from surfaces and objects [23]. A recent paper by Matteo Bassetti's group investigated the incidence of pneumonias, which he called *ventilator associated pneumonia* (VAP), caused by HAI-infected ventilator devices [3]. Interestingly, Nasrin Hanifi and colleagues reported that ozone, via ozonated water, removed SARS-CoV2 from any surface and was much more able to reduce VAP incidence in COVID-19 patients than chlorexidine [24]. The use of ozone is much more effective than standardized disinfectants for critical care units such as ICUs. For example, while chemical compounds can reduce the presence of *P. aeruginosa* from 1.17 to 1.63 log (i.e. from 92.93–97.31% CFU/cm^2), ozone reduces this Gram negative bacterial biofilms from surfaces to 7.34 log (i.e. 99.99999% CFU/cm^2) [23]. Ozone is able to eradicate bacteria from ICUs as well as SARS-CoV2.

An interesting paper by Murata et al., demonstrated that 1.0 ppm ozone for 60 minutes, reduces viral replication of SARS-CoV2 on VERO6/ E6/TMPRSS2 infected cells from $1.7x10^7$ PFU/ml to $1.7x10^4$ PFU/ml (1,000 times) and that this reduction reached the value 10^3 PFU/ml with 6 ppm ozone for 55 minutes, considering that experimental controls introduced in the system lowered of only 2,000 times less [25]. A study from Le Hoang Tu and colleagues reported that a dose of 5 ppm ozone reduced fungi in Sabouraud dishes within 30 min of gaseous ozone exposure and Gram positive bacteria within 60 minutes, from 500 CFU/ml to zero [26]. The efficacy of some previously reported methods, to decontaminate ICUs, should be thoroughly revised [27].

Conclusions

Hospital acquired infections represent a serious concern in COVID-19 pandemic. As more than 85% of people dead for COVID-19 in Italy were elderly people with ages higher than 65–70 years old, with one or more age-related co-morbidities, HAIs should be one of the utmost warning for medical science and politics. Current managing pandemic with yellow, orange and red zones, stressing the common civil and socio-economic life, never expanding any serious debate about the role of HAI in exacerbating and dramatically increasing COVID-19 caused deaths, may result in a tremendous failure.

Declarations

The authors state they have no conflict of interest

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Figures

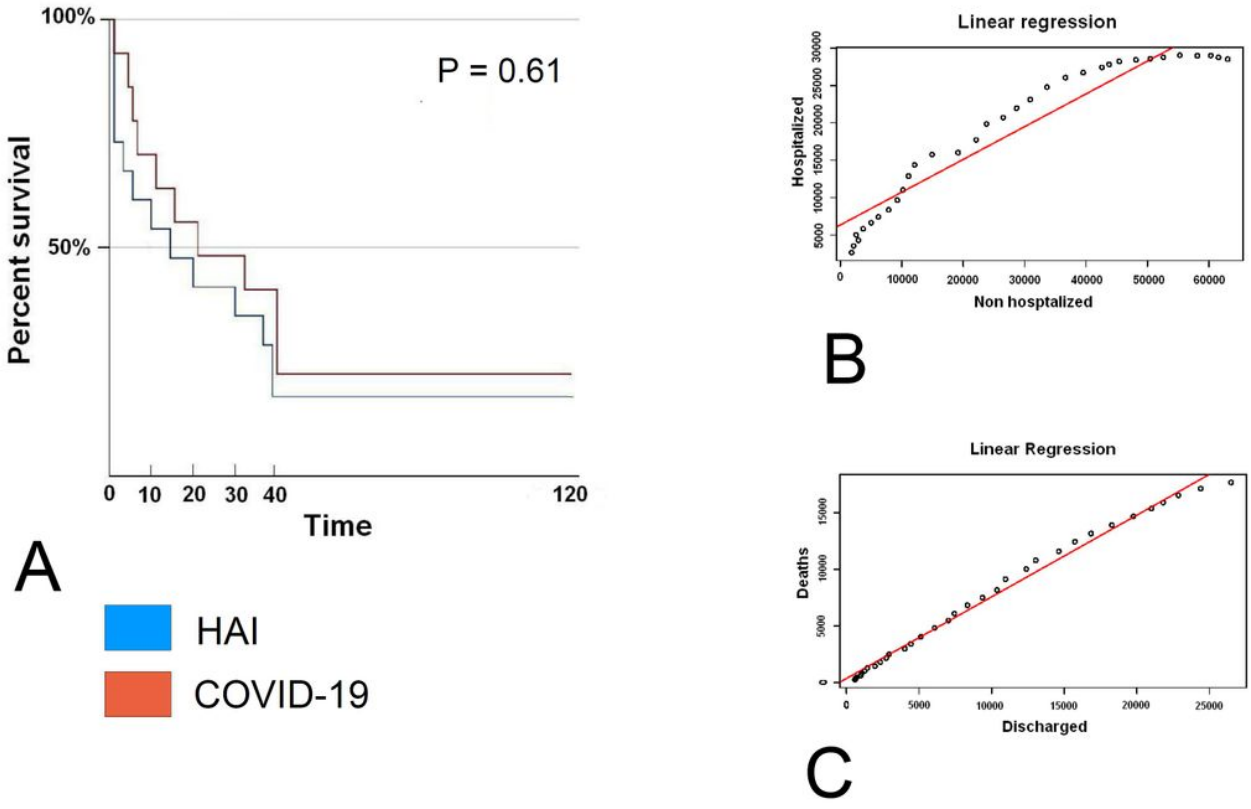

Figure 1

A) Kaplan-Meier survival % plot of HAI (calculated as the 7.84% fraction of deaths in hospitalized cohorts of patients for each day in the period March 8th 2020-Jume 8th 2020, blue) and COVID-19 (red). Data collected from the Italian Ministry of Health, publicly available. B) Linea regression plot of number of deaths in subjects undergoing hospitalization respect to the ones assisted in their homes and C) Linear regression plot of the number of estimated deaths versus discharged people during the lockdown period.

Both B and C panels refer to data from March 8th 2020 to April 8th 2020. Softwares STATA vers 16.1, StatPlus 2019.