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Age-adaptive and gender-balanced social interventions might be stepping stones to the next 'new normal' in COVID-19 outbreak

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Abstract

Many governments particularly in Europe are designing social interventions for the first post COVID-19 emergency phase. Definition of a 'best practice' for restriction release is urgent. Although data uncertainty generate difficulties, we believe near term analysis must shift from attempting to understand the numerous 'unknowns' to the clarification and interpretation of the few 'knowns', to create stepping stones towards rapid evidence-based decision making.

Here, open access data on COVID-19 severity in three European countries were analyzed. Spain's data were more comprehensive than those from Italy and Germany. Overall, COVID-19 severity shows a remarkable nonlinear growth with age that is significantly higher in adult males. Hence, age-adaptive and gender-balanced social interventions might represent efficient repopulation options for public health policymakers. Furthermore, we urge wider governmental effort for open access to relevant data. Their analysis will allow consolidation of existing trends, validation of key observations and thus facilitation of timely decisions.

Introduction

Several countries now face the beginning of the first post COVID-19 emergency phase. This is a real-life experiment which aims to reestablish a productive and socially acceptable environment after government-imposed lockdowns have successfully mitigated viral spread and "flattened the curve"[1]. There are many unknowns which make this recovery phase and its strategy difficult to define. Indeed, the speed and extent of COVID-19 spread to attain pandemic status has challenge existing health management systems of many countries across the world. In Europe, for instance: Italy[2], Spain[3] and UK[4] have been facing a healthcare crisis. The post COVID-19 emergency phase begins when a healthcare system returns to routine operating standards of care. This includes both emergency and ICU[2] but also the unwinding of surgery and diagnostic procedure backlogs. The process begins with a gradual re-introduction of population movement post lockdown.

In the current study, we analyze existing data on COVID-19 severity in three European countries, and propose a risk-categorization of likeliness to develop a severe COVID-19 form which requires ICU or is indicative of a higher risk of dying. Our study aims to provide guidance to decision makers on elements which may support an evidence-based repopulation strategy and identify existing knowledge gaps which

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could be easily filled with more complete open access to current data, and could be improved by harmonized data collection and analysis.

Data Analysis

In this section, a binomial test (N = # females + # males; k = # males; p=1/2) is applied to discrete integer data (confirmed cases, hospitalizations, ICUs, deaths) in order to assess whether the difference between female and male occurrence is significant at each age strata, and all p-values in a plot are Bonferroni-corrected for multiple hypothesis testing. Derived measures such as ICU/hospitalization ratio and naïve case fatality rate are not subject to binomial test for gender unbalance.

Fig.1 reports the age and gender analysis of data for the Spanish COVID-19 outbreak as of April 13, 2020. Open access data from the Ministry of Health of Spain[5] are used. The number of confirmed cases in Fig.1A shows that female infections is significantly ($p<0.05$) higher than male infections in age range categories 20-59 and 80+. This pattern is reversed in the age range 60-79 where male's infection is significantly ($p<0.05$) higher. However this information is known to be incomplete given the unknown number of undetected and the large portion of asymptomatic cases[6]. The clinical peculiarities of COVID-19, the lack of harmonized testing protocols and total absence of serological surveillance[7] are drivers that make currently available data on number of confirmed infections difficult to use and to interpret.

Notwithstanding these hurdles, the goal of this study is to highlight strong evidences associated with COVID-19 severity, with the aim to support guidance on useful outbreak-personalized social interventions for the second phase following the lockdown. In this regard, the information that emerges from the number of hospitalizations (Fig.1B) and number of ICU (Fig.1C) is the most relevant. Remuzzi et al.[2] stressed the importance of finding immediate solutions for countries with reduced health system capacity (such as Italy or Spain) to effectively respond to the needs of patients who are infected and require intensive care. From our analysis, it emerges that in Spain approximatively the 68% of hospitalizations (Fig.1B) and 67% of ICU (Fig.1C) are associated to the age range 60+ and that, regardless of age, the healthcare demand in terms of capacity is significantly ($p<0.05$) higher for males than for females. This may be due to the fact that males are at risk of developing more severe COVID-19 infections in particular in the age range 40+. It is notable that the number of deaths in the range 0-39 (Fig.1D) is very low (0.57%) and without gender unbalance. In the range 40-59, deaths increase to about 4% of the overall total whilst in 60+ age category, the death total climbs to around 92% of all deaths recorded. This trend is also confirmed by the naïve case fatality rate (Fig.1F) that exceeds the 1% threshold in the 40+ age range category. Altogether, these results suggest that the 60+ age range is at higher risk than the rest of the population, hence may generate the larger healthcare demand, due in major part to healthcare requirements of males, which is significantly higher than females. The age range 40-59 is moderately at risk but a significant ($p<0.05$) gender discrepancy is confirmed also in this case. Interestingly, from the ICU/hospitalization rate (Fig.1E) it emerges that although very few cases required hospitalization in the 0-9 age range category, those that did were more likely to require ICU compared to juvenile and middle age strata.

Fig.2 reports the age and gender analysis of all openly available data for the Italian COVID-19 outbreaks as of April 10, 2020 and the German outbreak as of April 12, 2020. Open access data from the Italian Superior Institute of Health[8] and the German Robert Koch Institute[9] respectively are used. The number of confirmed cases in Italy (Fig.2A) shows that female infections seems significantly ($p<0.05$) higher than male infections in age ranges 20-49 and 90+. This is largely in agreement with the Spanish results shown in Fig.1A. The pattern is reversed in the age range 50-79 where male infections is significantly ($p<0.05$)

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higher, again in agreement with the Spanish data. The results from Spain and Italy are not in agreement for age ranges 50-59 and 80-89. The findings support the need to perform a random COVID-19-wide screening of the contagions in the population of different countries[7]. The number of deaths in Italy (Fig.2B) and Germany (Fig.2D, the available open access data for Germany report only the age strata 59- as a unique range) confirms the age/gender trend and the percentages obtained for the Spanish population. The naïve case fatality rate for Italy (Fig.2C) displays a nonlinear age-growing trend and gender unbalance similarly to the results in Spain (Fig.1F).

Discussion of the proposed social interventions

At the beginning of the COVID-19 outbreak in China, specific knowledge in relation to the nature of the pathogen, the rate of spread through populations and the clinical disease progression was lacking. Therefore, a stay-home (lockdown suppression) strategy was the only reasonable solution available to authorities. We still lack data[6] on many aspects of COVID-19, but two clear facts from data generated from the epidemic have emerged. The first fact is that data from Spain, Italy and Germany underpin that COVID-19 severity has a remarkable nonlinear growth with the age. Thus we propose that the severity of social interventions should grow nonlinearly with age to optimize their efficiency. The second fact is that COVID-19 severity is significantly ($p<0.05$) higher in males than females in the dataset analyzed. This gap is particularly large in the age range 40+, and therefore we suggest that gender-balanced repopulation after lockdown should be encouraged. The design of new COVID-19-personalized social intervention strategies that utilize the learnings from these and other data, such as relevant comorbidities, may contribute to saving human lives, reducing healthcare costs and facilitating a more rapid return to economic sustainability.

Open access data currently available from most countries are inadequate if a comprehensive study to define gender and age susceptibility to COVID-19 is to be performed. In particular, data on hospitalizations and ICU admissions (which are crucial in data analysis for COVID-19 decision making[2]) are not easily accessible. In order to gain the most robust evidence and develop accurate guidelines to support policy makers, it is imperative that the scientific community is able to rely on harmonized and interoperable open access data. Nevertheless, in emergency scenarios with reduced data available, the medical and scientific communities should use all data potential to rapidly move from generic social intervention strategies towards outbreak-tailored approaches. In the era of personalized healthcare, future outbreak precision strategies should act in a coordinated fashion and on different levels, by integrating different large-scale social interventions[10] with medium-scale active surveillance[11] and small-scale contact tracing[12].

Conclusion

In our study, both age and gender are variables that clearly influence the clinical outcomes of COVID-19. Individuals in the 0-59 age range and females are significantly less likely to develop a severe condition and die, whereas adult males in the age range 60+ are more likely at risk of severe disease. Thus, considering an age-adaptive and gender-balanced repopulation during the first post COVID-19 emergency phase would seem a public health empowerment opportunity. Meanwhile, a graded shielding protocol for categories at risk, including children with underlying conditions, should be considered regardless of age and gender. This conceptual framework could then be tailored with single country data which may positively affect clinical outcomes.

COVID-19 has found an unprepared world. We are working under extreme emergency conditions with little time to think and react. The harmonization, validation and verification of raw data is of the utmost

importance but require time that is not always available to decision makers. In the meantime, we can provide stepping stones of scientific–based evidence to get us from the rough early times of a complex health emergency to the next 'new normal'.

Contributions

CVC and IC conceived the study. CVC is responsible for data analysis, figure design and writing of the manuscript. IC is responsible for writing of the manuscript.

Declarations of interest

We declare no competing interests.

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Figures

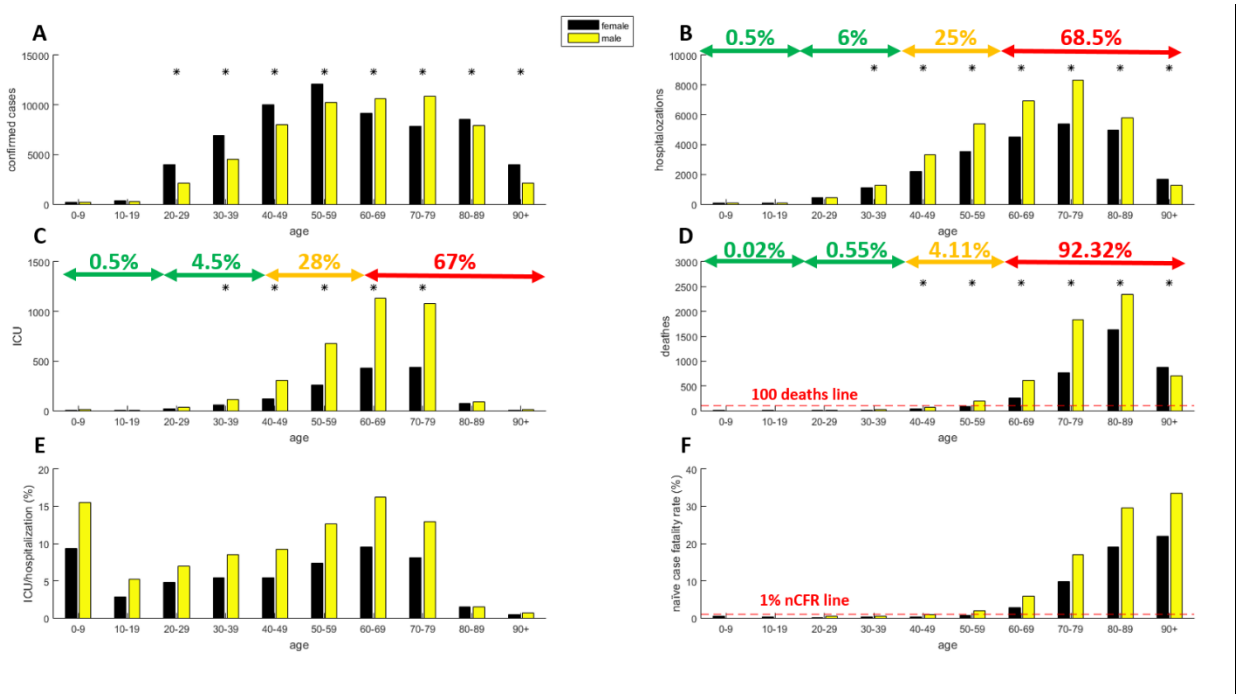

Figure 1. Data analysis of Spanish COVID-19 outbreak at April 13, 2020. For panels A, B, C, D the presence of a star on top of a specific age strata indicates that the difference between female and male occurrence is statistically significant ($p<0.05$) according to binomial test.

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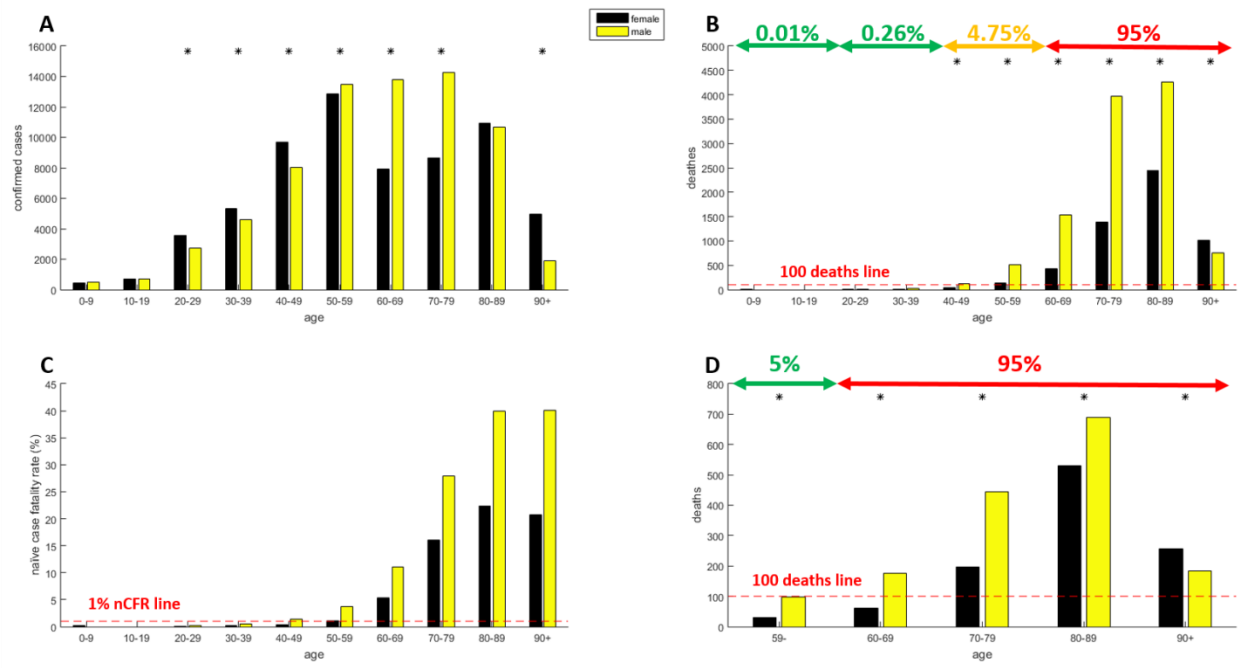

Figure 2. Data analysis of Italy and Germany COVID-19 outbreak. (A-C) data of Italian outbreak at April 10, 2020. (D) data of German outbreak at April 12, 2020. For panels A, B and D the presence of a star on top of a specific age strata indicates that the difference between female and male occurrence is statistically significant ($p<0.05$) according to binomial test.