

EDITORIAL



Why and how do we need comprehensive international clinical epidemiology of ARDS?

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One of the most evident weaknesses of scientific and public health strategies in the management of the coronavirus disease 2019 (COVID-19) pandemic is certainly the scarcity of robust epidemiological data, not limited to the quali-quantitative descriptions of patient populations and their outcomes, specifically in the hardly comparable ICU settings of care [1–3], but aimed at what has become the core and the vocation of a clinically oriented epidemiological investigation. Clinical data collected and analysed with sound methodological criteria are the essential source of information, closely complementary to physiopathological data for a better understanding of the causes of the outcomes of critical and still uncertain clinical conditions.

The substantial absence of this type of epidemiology has suggested a broader question: whether and how far the failure documented in publications relating to the ICU phases of Covid-19 coincides with the state of the art also for the acute respiratory distress syndrome (ARDS), closely overlapping the severe pulmonary involvement seen in a small but dramatic fraction of the Covid-19-infected population.

We felt that a targeted survey of the clinical epidemiological literature could provide an overview of the methodological strengths and weaknesses of recent research, and serve as an informed suggestion as to most practicable strategies.

The main general results are summarised in Table 1 (the detailed bibliography examined is accessible on request), while the comments that follow underline the

points which could be considered priority targets in the future.

Papers published to celebrate the 50th birthday of ARDS as a specific clinical entity and diagnosis show a clear consensus[4–7]: ARDS should become a model scenario to test the passage from the classical strictly descriptive estimates of its incidence and mortality (e.g., 10% of all ICU cases, 23% of all mechanically ventilated patients, 5.5 cases/ICU bed/year, 40% in-hospital mortality), to systematic monitoring of unmet clinical and technological needs in different care settings. The few long-term clinical studies reflect the practice in selected centers hardly representative of the broader spectrum of ICUs, and do not give a reliable epidemiological profile of ARDS based on hard clinical outcomes.

Surprisingly, administrative databases, which have been the truly innovative protagonists of epidemiological information in all major areas of medicine, appear in only two contributions, both from the USA, with the classical indicators of population-based trends of incidence and prevalence of events and their short-term outcomes [8, 9]. Meta-analyses, which include just the selected trial populations, can only be used as retrospective epidemiological tools, suffering similar substantial limitations.

A closer look at the most recent publications on ARDS (from 2015 onwards) does not really add much to our epidemiological knowledge, with the important exception of a formally planned project promoted by an international network of ICU clinicians [10] which makes important comparisons of the characteristics and the short-term outcomes of patients over a broad spectrum of countries and settings. A chapter that is confirmed as a marginal topic of research interest, despite important anticipations and suggestions [11], is the long-term outcome and burden of care of the ARDS survivors in the ICU [12].

A forward-looking interpretation of the above survey seems to confirm the structural and cultural reasons that

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Table 1 Outline and findings of the literature search: 2015–2019

Keywords: ARDS, Epidemiology, Mortality, ICU population

Quantitative findings: 1365 overall; 165 full-text articles assessed for eligibility; 41 studies included in qualitative synthesis (28 original articles, 13 systematic reviews and meta-analyses).

Evidences: The majority of studies cover retrospective or prospective analyses of monocentric or paucicentric series of cases included on the basis of widely heterogeneous criteria, analysed mainly descriptively, with no well-specified protocols to explore causal associations with contextual clinical care determinants of mainly in-hospital mortality.

Weaknesses and gaps: Absence of any stable and/or formal national, regional, international network (neither supported nor promoted by public actors or scientific societies) to describe, monitor, assess comparatively and periodically the characteristics and the determinants of the outcomes of the overall ARDS populations and of their main clinical sub-populations.

make epidemiological research particularly difficult in intensive care and ARDS. The acute, intensive attention to complex clinical conditions, not easy to standardise, is certainly very demanding, relegating epidemiological research and the related data collection to a strictly occasional role. Because of its feared formal requirements of rigid pre-definition of the criteria required for reliable population analyses, an epidemiological approach seems an extra burden to be added to the already heavy tasks of clinical care, as well as of physiopathological and therapeutics-oriented research.

The scarcity of large multicenter and multi-country epidemiological studies during the long period of the pandemic which has, however, seen the flexible and innovative implementation of population trials on treatments and vaccines seems to confirm the cultural distance between ICUs and comprehensive, real-time, not simply descriptive and retrospective, epidemiology.

ARDS is part of this prospective, as model scenario, which should be reproduced for other critical conditions where planned complementarity of epidemiological and clinical information is expected to be highly effective in generating new knowledge and improving care. Sepsis [13] and septic shock [14] are a couple of similar priority areas for implementing the strategies summarised in Table 2 and commented below.

Well planned utilization of the many administrative databases which are uniquely interesting components of the 'big data' world (where research investments and resources too are promised) is a priority. International cooperation in data sharing and comparative analyses

must be a duty of scientific societies, in close collaboration with public authorities, to assure reliable, representative information to the general public on topics such as the ongoing pandemic. This meets their right to be briefed not just on how and where they die, but on what can be done to guarantee their health and life.

Networking between clinical centres must be promoted to assure the independent nested integration of the administrative databases with the spectrum of physiopathological, clinical, diagnostic-therapeutic, and managerial information, with a view to comparing the many diversified determinants of different outcomes [15]. International networks need to be established to give visibility to the increasingly recognized, but easily forgotten or not adequately investigated, inter- and intra-countries inequalities and other differences.

A further, complementary and much needed epidemiological instrument is the construction, starting from and linked to the above databases, as well as ex novo, of predefined cohorts of the many sub-populations that must be considered as parts of the overall population 'diagnosed' as Covid- or non-Covid-related ARDS. An accurate age-stratified approach, for instance, is indispensable, not simply as an obvious component of the often scantily informative multivariable approaches, but to explore in depth the clinical evolution of the disease with age.

A specific focus on the characteristics and the burden of long-term care and mortality of Covid or no-Covid ICU survivors is an important objective, calling for close integration of administrative and clinical databases [16].

Table 2 Steps and strategies towards comprehensive ICU clinical epidemiology (CE)

Recognition of epidemiology as an integral component and resource in the ICU providing representative samples of the variability and comparability of the known, and the undefined, sub-populations about which innovative knowledge is required

Stable/permanent CE networks of ICUs representative of national, regional, international research interests

Scientific societies as the 'natural' promoters of networks/projects to be supported with public and private general and problem-targeted grants

Linkage and sharing of parallel or nested administrative, clinical, and basic research databases flexibly oriented toward predefined goals/clinical conditions

Definition of better targeted legal rules for the accessibility and sharing of individual patients' data.

Our substantial ignorance on this important component of the post-acute phases of ARDS is one of the major gaps to be filled for an original contribution of epidemiology to the quality of care and innovative research not only for ARDS, but for the whole spectrum of clinical conditions and the ICU.

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Declarations

Conflicts of interest

GT and LV attest that they have no conflicts of interest. AP reports personal fees from Maquet, Novalung/Xenios, Baxter, and Boehringer Ingelheim, outside of the submitted work.

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