The Economic Impact of a PEEP-based Lung Recruitment Clinical Trial Programme in Patients with Acute Respiratory Distress Syndrome

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Research Article

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is one of the most challenging clinical conditions of the critical care medicine. Previous studies estimate the economic impact and the public return of the clinical trials on public health.

Methods: The ART was conducted through a multicenter randomized trial at 120 intensive care units (ICUs) from 9 countries from November , 2011, through April, 2017, enrolling adults with moderate-to-severe ARDS, which investigated whether lung recruitment associated with PEEP titration according to the best respiratory-system compliance decreases 28-day mortality of patients compared with a conventional low-PEEP strategy. This paper identifies the economic impact of the clinical trial from the value of lives saved if the trial findings were implemented in the eligible patient populations for one year, and then computes the public return by subtracting the relevant clinical trial costs from the gross benefit. The economic impact was computed by subtracting the ART costs from its gross benefit.

Results: The net benefit of the ART is approximately 152 millions of dollars if the ART findings is implemented in 50% of the eligible patients in Brazil, under the baseline assumptions. Moreover, for every dollar spent in the clinical trial, a return of 114 dollars was achieved in Brazil alone. If the ART's trial findings were implemented in all eligible patients, then a return of the trial would be 229.5 dollars for every one dollar invested, and net benefit would be around 304 millions of dollars.

Conclusions: These findings highlight the substantial economic benefit of clinical trials on ARDS treatments for the society. It also points out that the public return of clinical trials can be potentialized when the new trials' findings are fully implemented on eligible patients. Efforts should be made to integrate clinical trials findings with the frontline health care delivery.

1. Introduction

Acute respiratory distress syndrome (ARDS) is one of the most challenging clinical conditions of the critical care medicine[1]. The pneumonia associated with the novel coronavirus (COVID-19) evolves to ARDS in the most severe cases. Consequently, ARDS is a major cause of need of invasive mechanical ventilation and death in COVID-19[2]. Several clinical trials have assessed the effect of treatments to reduce mortality rates of patients with ARDS[3]. However, no study evaluates the economic benefits and the public return generated by clinical trial-based protocols on the treatment of patients with ARDS.

Previous studies estimate the economic impact and the public return of the clinical trials on public health. Johnston et al.[4], for instance, investigate the effect of a US National Institutes of Health programme of clinical trials on public health and costs. HERG[5], Glover et al.[6], and Glover et al.[7] estimate, respectively, the returns to United Kingdom of the publicly funded cardiovascular (CVD), cancer and musculoskeletal disease (MSD) research. ACTA[8] assesses the overall health and economic impact of investigator-initiated clinical trials conducted by select clinical trials networks in Australia. Pham et al.[9] compare the health

and economic impacts of the randomized clinical trials (RCTs) of Australia and New Zealand. Luce et al.[10] estimate the return on US investment in overall health.

This study estimates the economic impact of the protocol indicated by the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART)[11]. The ART was a clinical trial conducted by the Brazilian Research in Intensive Care Network (BRICNet) which investigated whether lung recruitment associated with PEEP titration according to the best respiratory-system compliance decreases 28-day mortality of patients with moderate to severe ARDS compared with a conventional low-PEEP strategy.

2. Methods

2.1. Methodological Approach

This paper identifies the economic impact of the clinical trial from the value of lives saved if the trial findings were implemented in the eligible patient populations for one year, and then computes the public return by subtracting the relevant clinical trial costs from the gross benefit.

The Potential Impact of the Trial on an Individual Patient's Health. The main finding of the ART is the 28-day mortality rate of 55.3% in patients with moderate to severe ARDS treated with lung recruitment and titrated PEEP compared to 49.3% in patients treated with low PEEP. Further, it also indicates that an individual ARDS patient's chance of surviving increases in 5.95% if all ICUs had stopped using recruitment maneuver procedure since the ART findings became public and started using only low PEEP protocol.

Note that if no ICUs used to adopt lung recruitment maneuver and PEEP titration protocol in ARDS patients before the ART, then the potential impact of trial on individual's health will be null as the trial will not induce any change in clinical procedure of ARDS patients.

Individual's Mortality-Avoidance Adjusted Value of Life. Note that, as the trial shows that an individual ARDS patient can increase the chance of surviving by 5.95% when treated with the appropriate protocol, the life value of an individual in that heath conditions also increases by that amount.

This study estimates the value of life using the Value of a Statistical Life (VSL) approach[12–13]. The VSL of an individual is determined by the present value of this individual's market productivity. As an individual productivity is convertible in labor market income, the statistical life value of an individual corresponds to the present value of the stream of all future labor income.

As this paper aims at evaluating the economic impact of the ART, it only estimates the value of life of an individual with the same characteristics as the ones in the clinical trial, which is a 51 years-old individual.

The next step is to determine the monetary value of the impact of the trial on an individual patient's health. It corresponds to the individual benefit of the trial's finding, which is defined hereafter as the individual's mortality-avoidance adjusted value of life.

Identification of the Number of People Potentially Affected. To estimate the potential economic impact and public return of the trial for the society, one needs to identify of the number of people potentially affected.

The number of people potentially affected in a year is obtained by combining the incidence rate of ARDS and the population in Brazil.

Value of Potential Lives Saved. The value of potential lives saved is the individual's mortality-avoidance adjusted value of life multiplied by the number of people potentially affected in a year if the trial findings are implemented in all eligible patients.

The value of potential lives saved, and the effective value of lives saved would be the same. For this reason, this paper compute two key measures of the gross benefits of the trial: the potential gross benefit and the effective gross benefit of the trial (supplemental materials)

Net Benefit and Benefit-Cost Ratio. The economic impact of the trial is computed as net benefit of the trial. This is computed by subtracting the effective gross benefit, in Eq. (2), from the clinical trial costs.

The benefit-cost ratio is obtained by dividing the net benefit by the clinical trial costs. The benefit-cost ratio measures the public return in dollars of the clinical trial findings for every dollar invested.

2.2. Data

This study uses the relevant data from Brazil as the trial was conducted with public funds provided by the Brazilian Ministry of Health. All the monetary benefits and costs in this study were computed in Brazilian Reais, and then converted in U.S. Dollars of December 2019, which is the most recent period for which there is information for all the relevant data for this paper.

As previously described, to estimate the value of life of an individual with the same characteristics as the ones in the clinical trial, a 51 years-old individual, three pieces of information are required: (i) life expectancy of a 51 years-old individual, (ii) all expected future labor income of a 51 years-old individual from his 52nd year of life to his last expected year of life, and (ii) a discount rate to compute the present value of the future labor income streams.

Information on life expectancy of a 51 years-old individual in Brazil is 30 years[14]. For the expected future labor income of a 51 years-old individual, this study uses the annualized average monthly labor income of all individuals who are between 51 years-old and 81 years-old (which is the last expected year of life of an individual who is 51 years-old)[15]. For this, it was used the values of December 2019. As a discount rate, it was used SELIC rate of December 2019, which was 4.5 % per year. SELIC rate is basic interest rate defined by the Central Bank of Brazil. To convert, the value of life in U.S. dollars, it was used the official average Dollar-Brazilian Real exchange rate of December 2019, which was 4.12 Brazilian Reals per dollar.

To compute the number of people potentially affected in a year, information on the incidence rate of ARDS and on the Brazilian population are needed. Incidence rate was obtained from Li et al.[16] which

finds that the 2008 incidence rate (per 100,000 person-year) of moderate and severe ARDS is 38.3. According to the Brazilian Institute of Geography and Statistics (IBGE), the Brazilian population in 2019 was 210,147,125 habitants.

3. Results

3.1. First Elements

The estimated the value of life of an individual with the same characteristics as the ones in the clinical trial is 127,696 dollars. Note that if an individual has ARDS and is treated with lung recruitment maneuver and PEEP titration protocol, then the patients has 44.7 percent of chance of surviving[11]. Therefore, this individual ARDS patient's expected value of life becomes 57,080 dollars. Equivalently, if an individual has ARDS and is treated with conventional low PEEP protocol, has 50.7 percent of chance of surviving. Hence, this individual ARDS patient's expected value of life becomes 64,678 dollars.

The individual's mortality-avoidance adjusted value of life corresponds to the difference between the expected value of life of an individual treated with conventional low PEEP protocol and the expected value of life of an individual treated with lung recruitment maneuver and PEEP titration one. It corresponds to 7,598 dollars.

As the number of people potentially affected in a year is equal to 80,486 individuals, the value of potential lives saved can be calculated. The value of potential lives saved is equal to 611,528,960 dollars per year.

3.2. Main Results

The first result presented in this subsection is the potential gross benefit of the trial. Table 1 shows that if the pre-trial fraction of high PEEP in ICUs was 50 percent, then the potential gross benefit of the trial is around 305 millions of dollars. The pre-trial fraction of high PEEP in ICUs equal to 50 percent corresponds to the base case assumption of this study.

TABLE 1 - The Potential Gross Benefit of the Trial

Pre-Trial Fraction of High PEEP in ICUs (%)	Potential Gross Benefit (U.S. Dollars) Incidence rate (Li at al., [16])
100	611,528,960
90	550,376,064
80	489,223,168
70	428,070,272
60	366,917,376
50	305,764,480
40	244,611,584
30	183,458,688
20	122,305,792
10	61,152,896
0.2	1,327,018
0	0

ICUs (Intensive care units).

Table 2 presents the effective gross benefit of the trial for different fraction of ICUs that have stopped using recruitment maneuver protocols.

TABLE 2 - The Effective Gross Benefit of the Trial

Fraction of ICUs stopped using High PEEP Protocol after the ART (%)	Effective Gross Benefit (U.S. Dollars) Incidence rate (Li at al., [16])
100	305,764,480
90	275,188,032
80	244,611,584
70	214,035,136
60	183,458,688
50	152,882,240
40	122,305,792
30	91,729,344
20	61,152,896
10	30,576,448
0	0

Table 2 shows that if the pre-trial fraction of high PEEP in ICUs and fraction of ICUs that have stopped using recruitment maneuver procedure since ART became public are both 50 percent, then the effective gross benefit of the trial is around 152 millions of dollars.

The clinical trial costs amount to 1,326,411 dollars. Hence, the net benefit of the trial under the assumptions of Table 2 are described in Table 3 below.

TABLE 3 - The Net Benefit of the Trial

Fraction of ICUs stopped using High PEEP Protocol after the ART (%)	Net Benefit (U.S. Dollars) Incidence rate (Li at al., [16])
100	304,438,069
90	273,861,621
80	243,285,173
70	212,708,725
60	182,132,277
50	151,555,829
40	120,979,381
30	90,402,933
20	59,826,485
10	29,250,037
0.4	0.0
0	-1,326,411

ICUs (Intensive care units); ART (Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial).

Based on the base case assumptions that the pre-trial fraction of high PEEP in ICUs and fraction of ICUs that have stopped using recruitment maneuver procedure since the ART findings became public are both 50 percent, then the net benefit of the trial is around 151 millions of dollars.

Note also that if no ICUs have stopped using recruitment maneuver procedure since the ART findings became public, among the ones that used to adopt such protocol in ARDS patients, then effective gross benefit is zero (Table 2) and the net benefit is negative (Table 3). On the contrary, if the ART findings were implemented in all ICUs (100 percent) that previously used the lung recruitment maneuver and PEEP titration protocol, then the net benefit of the trial would be approximately 304 millions of dollars.

Table 3 also shows that the results of the ART findings needs to be implemented in only 0.4 percent of ICUs that previously used the lung recruitment maneuver and PEEP titration protocol for benefits to exceed costs (under the base case assumption that the pre-trial fraction of high PEEP in ICUs was 50 percent).

Lastly, the benefit-cost ratio, which is the ratio between net benefit and the clinical trial costs, is computed. Table 4 shows that the benefit-cost ratio of the trial for different pre-trial fraction of high PEEP in ICUs and different fraction of ICUs that had stopped using high PEEP since the ART findings became public.

TABLE 4 – Benefit-Cost Ratio

		Fraction of ICUs stopped using High PEEP Protocol after the ART (%)						
		0	20	40	50	60	80	100
Pre-Trial Fraction of High PEEP in ICUs (%)	0	-1.0	-0.8	-0.6	-0.5	-0.4	-0.2	0.0
	20	-1.0	17.4	35.9	45.1	54.3	72.8	91.2
	40	-1.0	35.9	72.8	91.2	109.6	146.5	183.4
	50	-1.0	45.1	91.2	114.3	137.3	183.4	229.5
	60	-1.0	54.3	109.6	137.3	165.0	220.3	275.6
	80	-1.0	72.8	146.5	183.4	220.3	294.1	367.8
	100	-1.0	91.2	183.4	229.5	275.6	367.8	460.0

ICUs (Intensive care units); ART (Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial).

Table 4 shows that under the base case assumption (the pre-trial fraction of high PEEP in ICUs and the fraction of ICUs that have stopped using recruitment maneuver procedure since the ART findings became public are both 50 percent), the benefit-cost ratio is around 114 dollars. That corresponds to a public return of the trial of 114 dollars for every one dollar invested. Table 4 also shows that if the ART findings were implemented in all ICUs that previously used the lung recruitment maneuver and PEEP titration protocol, then a return of 229.5 dollar for every one dollar invested.

3.3. Sensitivity Analysis

Sensitivity analyses are used to investigate what would happen to the results if major assumptions used in calculations were to change. The following assumptions were tested through sensitivity analyses: a different estimated number of people potentially affected (moderate to severe ARDS incidence) in a year, and different values of statistical life.

Different estimated number for people potentially affected in a year. A sensitivity analysis of the public return of the trial is conducted by using moderate and severe ARDS incidence rate obtained by Caser et al.[17]. They found that the annual incidence rate (per 100,000 person-year) of moderate and severe ARDS is 6.3.

Table S1 in the Supplementary shows that the results of the ART findings need to be implemented in only 2.6 percent of ICUs that previously used the lung recruitment maneuver and PEEP titration protocol for benefits to exceed costs (assuming that pre-trial fraction of high PEEP in ICUs was 50 percent). It also shows that under the base case assumption, then the benefit-cost ratio is around 18 dollars. That corresponds to a public return of the trial of 18 dollars for every one dollar invested. This sensitive

analysis shows that the public return of trial is still remarkably high even when considering a low incidence rate of moderate-to-severe ARDS.

Different Values of Statistical Life. Table 5 presents these different studies and provide country-specific references of the value of a statistical life. Brito[18] estimated the value of statistical life is 173.128.13 dollars. Yet, Ferrari et al.[19] estimated the VLS in Brazil is equal to 119.687.02.

TABLE 5 – References of Value of Statistical Life

Reference	Country	VSL (US$ 2019)
Brito [18]	Brazil	172,128.13
Ferrari et al. [19]	Brazil	119,687.02
Mahmud [20]	Bangladesh	4,069.54
Bhattacharya et al. [21]	India	191,668.42
Iragüen e Ortúzar [22]	Chile	225,409.33
Yang, Liu and Xu [23]	China	1,119,432.27
Krupnick et al. [24]	Canada	1,276,320.62
Svensson [25]	Sweden	3,552,509.74
Hensher et al. [26]	Australia	7,579,769.80

Based on Ferrari et al.[19] Value of Statistical Life, Table S2 presents the net benefit and the benefit-cost ratio of the trial for different fraction of ICUs that have stopped using recruitment maneuver procedure since the ART's findings became public.

Table S2 shows that the results of the ART findings need to be implemented in only 0.5 percent of ICUs that previously used the lung recruitment maneuver and PEEP titration protocol for benefits to exceed costs. It also shows that if the pre-trial fraction of high PEEP plus lung recruitment in ICUs and fraction of ICUs that have stopped using recruitment maneuver procedure since the ART findings became public are both 50 percent, then the benefit-cost ratio is around 107 dollars. This shows that the public return of trial using Ferrari et al.[19] Value of Statistical Life has the same magnitude of the public return obtained in a previous subsection (the base case assumption).

4. Discussion

Our results show that the net economic benefit of ART was 152 million dollars in one year, assuming a low PEEP strategy was used instead of lung recruitment and high PEEP strategy in 50% of eligible patients. In addition, for every dollar spent to fund the clinical trial, a return of 114 dollars was achieved in a year just in Brazil.

Note also the net benefit of the trial would be approximately 304 millions of dollars, if the ART findings were implemented in all ICUs that previously used the lung recruitment maneuver and PEEP titration

protocol. This points out that economic impact can be maximized if the new findings of trials are fully implemented on eligible patients.

The COVID-19 pandemics has reached almost 9 million cases worldwide[20]. Approximately 5% are severe cases with ARDS as the main clinical manifestation[21]. The number of lives saved and economic impact of a trial such as ART was probably largely amplified during this crisis.

Using a similar method, previous studies have estimated the economic impact and the public return of the clinical trials on public health. For instance, Johnston et al.[4] examine the impact of a US National Institutes of Health programme of clinical trials on treatment cost and public health. Based on 28 trials that costed 335 million dollars, they find that 21 percent of the trails (6 out 28) had improved in health, and 14% (4 out of 28) had reduced treatment cost. In a 10-years window, their estimates show the programme of trials saved about 470,000 quality-adjusted life years for 3.6 billion dollars in total cost (trial and treatment cost). By quantifying the value of the quality-adjusted life year as gross domestic product per-capita, the 10-years estimated net benefit of the trials' programme was 15.2 billion dollars. This is equivalent to 1,500 million of dollars per year, which corresponds to 58 million of dollars per year per trial.

This study differs from Johnston et al.[4] in important dimensions. First, it shows that the net benefit of ART is 2.62 times bigger than average net benefit of the 26 trials in US National Institutes of Health Programme in Johnston et al., 2006 (152 millions of dollars *versus* 58 millions of dollars). The difference between the net benefits of the two studies are resulted of following features: (i) a sizeable health impact on individual ARDS patient of the ART's finding, (ii) a relatively small cost of the ART compared to the ones analyzed in Johnston et al. (2006), and (iii) the fact that the two protocols in the ART (lung recruitment and titrated PEEP versus conventional low PEEP) have the same health costs while 88 % of the trials in Johnston et al. [4] increases heath care costs. Lastly, Johnston et al.[4] do not compute the potential public return if the trials' findings are fully implemented on eligible patients, a return computed in this paper. The estimation of the potential public return is important as it reveals the society gains of making efforts to integrate clinical trials findings with the frontline health care delivery.

Using a methodology like the one in this paper, Glover et al.7 compute the return in terms of net value of improved health outcomes from research expenses on musculoskeletal disease (MSD) research publicly funded by United Kingdom (UK). They find a benefit-cost ratio equals to 1.07 for MSD research, which corresponds to a return of 7%. Based on a different approach, HERG5 and Glover et al.6 rely on a top-down approach to estimate the internal rate of return from UK publicly funded medical research on cardiovascular diseases (CVD) and on cancer research. They find that a return of 9% and 10% from CVD and cancer research, respectively. A cost-benefit analysis shows a benefit-cost ratio of 1.09 (for CVD research) and 1.10 (for cancer research). These numbers indicate that benefit-cost ratio of ART is substantially larger than benefit-cost ratio of all these United Kingdom publicly funding medical research projects.

ACTA[8] investigates the economic and the overall health impact of 25 high-impact clinical trials conducted by a three clinical trial networks in Australia. ACTA[8] shows that if these trials were implemented for one year in 65% of the eligible patient populations in Australia, then: (i) a return of $51.10 is achieved for every $1 granted in National Health and Medical Research Council (NHMRC) awarded to the 25 analyzed trials, (ii) the total benefit-to-cost ratio is 5.8 for the three analyzed networks, (iii) the benefits of trials exceed their costs if the findings of 25 analyzed trials are implemented in 11% of the eligible patient populations, and (iv) measured in terms of health improvement and health service cost reduction, the gross benefit would be approximately $2 billion.

A comparison between ACTA[8] findings and the results in this paper reveals important information. First, it shows that benefit-cost ratio of the ART is 2.62 times larger than the benefit-cost ratio of the 25 selected trials in ACTA[8] - a return of 114:1 was found for the ART *versus* 51.1:1 for ACTA's trials. Second, the ART needs to be implemented in a lower fraction of the eligible population (0.4 percent) than that the trials in ACTA[8], which is 11 percent. This reveals the substantial economic benefit and cost-effectiveness of the ARTs comparing to others.

By analyzing the economic and health impacts of different maternal and perinatal health cares, Pham et al.[9] compares innovative interventions and standard practices. They find a potential cost saving of $ 26.3 million over 5 years if the findings of the six most efficient interventions are implemented in 10% of the eligible populations. If they are implemented in 100% of the eligible patients, then the potential cost saving can reach $262.8 million. A comparison between the results in Pham et al.[9] and the ones in this paper reinforces our findings of the ART has high economic benefit and large cost-effectiveness.

This paper is also related to earlier studies that estimate health care's return on investment (ROI). For instance, Luce et al.[10] analyze the data of US overall investment in health care from 1980 to 2000 to estimate the return on investment in health care. They find that the return per dollar invested in health care ranges from 1.55 to 1.94 dollars. These figures reveal that of the ART is substantially larger than the investment in overall health-care services (a return of 114 dollars for each dollar invested was estimated for the ART).

This study has some limitations. First, it relies only on the ART clinical trial to draw conclusions about the economic benefit of clinical trials on ARDS treatments for the society. However, there is very important reason for evaluating ART: it is a study that proposes a protocol which is easy to implement in ICUs at a negligent cost and, more important, has a striking effect on ARDS patients' chances of surviving. Second, the analysis focused on Brazil since the initial trial investment was funded by the Brazilian government. Although the findings might not be generalizable elsewhere, since values of health vary widely across countries, the evaluation method proposed in this paper is applicable to other countries which wish to evaluate the economic impact of the ART clinical protocol recommendation. Besides, Brazil is a typical developing country where governments frequently face the dilemma between funding health care services or academic research on health. The results show that the economic return of health research is considerable high in a developing country, and it is higher than the return of health care if one takes the

returns computed by Luce et al.[10]. Third, the estimates of the value of the life may vary with the methods used for assessment, producing uncertainty in the overall economic value of the ART. However, the overall the public return of the ART has similar magnitude when considering other estimates for value of life.

5. Conclusions

Our findings highlight the substantial public economic return of funding clinical trials of treatments for critically ill patients in middle-income countries, such as Brazil. It also points to the potential of well-designed clinical trials improve health care quality through cessation of ineffective interventions. Moreover, public return of clinical trials can be potentialized when the new trials' findings are fully implemented on eligible patients. Hence, efforts should be made to integrate clinical trials findings with the frontline health care delivery.

Declarations

Ethics approval and consent to participate

All protocols are carried out in accordance with relevant guidelines and regulations. The trial and all the methods were approved by the research ethics committee of the coordinating institution (HCor Research Ethics Committee approval no. 172/2011) and by the research ethics committees of all participant sites listed below:

Argentina: Hospital Nacional Alejandro Posadas; Sanatorio Juncal; Sanatorio Las Lomas. **Brazil:** A.C.Camargo Cancer Center; Fundação Hospital de Clínicas Gaspar Vianna; Fundação Hospitalar São Sebastião; Hospital Municipal Dr José Soares Hungria; Hospital Adventista de Belém; Hospital Alemão Oswaldo Cruz; Hospital Bandeirantes; Hospital Barra D'Or:; Hospital Cônego Monte Raso; Hospital da Luz; Hospital das Clinicas da Universidade Federal de Goiás; Hospital das Clinicas da Universidade Federal de Minas Gerais; Hospital das Clinicas de Botucatu; Hospital das Clínicas Luzia de Pinho Melo; Hospital de Base de São José do Rio Preto; Hospital de Clínicas de Porto Alegre; Hospital de Urgências e Emergências de Rio Branco; Hospital do Círculo; Hospital do Coração-HCor; Hospital do Servidor Público Estadual de São Paulo; Hospital do Trabalhador; Hospital e Pronto Socorro Dr. Aristóteles Platão Bezerra de Araújo; Hospital e Pronto-Socorro 28 de Agosto; Hospital Escola Padre Albino - Faculdades Integradas Padre Albino-Medicina; Hospital Especializado Octávio Mangabeira: Hospital Estadual Dr. Jayme dos Santos Neves; Hospital Estadual e Pronto Socorro João Paulo II; Hospital Estatual Getúlio Vargas; Hospital Evangélico de Cachoeiro de Itapemirim; Hospital Evangélico de Londrina; Hospital Evangélico de Vila Velha; Hospital Geral da Vitória da Conquista; Hospital Geral de Roraima; Hospital Israelita Albert Einstein; Hospital Lifecenter; Hospital Marcelino Champagnat; Hospital Maternidade São Vicente de Paulo; Hospital Metropolitano de Urgência e Emergência; Hospital Moinhos de Vento; Hospital Municipal da Vila Santa Catarina; Hospital Municipal Dr Mario Gatti; Hospital Municipal Dr. Moysés Deutsch (M'Boi Mirim); Hospital Municipal São Francisco de Assis; Hospital Municipal São José de Joinville; Hospital Naval Marcílio Dias; Hospital Nereu Ramos; Hospital Nossa Senhora da Conceição; Hospital Novo

Atibaia; Hospital Primavera; Hospital Regional da Asa Norte; Hospital Regional de Mato Grosso do Sul Rosa Pedrossian; Hospital Regional Hans Dieter Schmidt; Hospital Samaritano de Governador Valadares; Hospital Samaritano de São Paulo; Hospital Samur; Hospital Santa Casa de Bragança Paulista; Hospital Santa Cruz; Hospital Santa Juliana; Hospital Santa Luzia; Hospital Santa Rosa; Hospital São José – Criciúma; Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul; Hospital São Lucas de Governador Valadares; Hospital São Lucas-FAG; Hospital São Luiz - Unidade Anália Franco; Hospital Saúde da Mulher; Hospital Sirio-Libanês; Hospital Unimed Araçatuba; Hospital Unimed Joinville; Hospital Unimed Santa Helena; Hospital Unimed Vitória; Hospital Unimed-Rio; Hospital Universitário Cassiano Antonio de Moraes da Universidade Federal do Espirito Santo; Hospital Universitário da Universidade Federal da Grande Dourados; Hospital Universitário do Oeste do Paraná; Hospital Universitário Pedro Ernesto; Hospital Universitário Polydoro Ernani de São Thiago; Hospital Universitário Regional de Maringá; Hospital Universitário Regional do Norte do Paraná; Hospital Universitário São Francisco de Paula; Hospital Universitário São Francisco; Hospital Vita Batel; Instituto de Infectologia - Emílio Ribas; Instituto do Câncer do Estado de São Paulo – ICESP; Irmandade da Santa Casa de Misericórdia de São Paulo; MEDIMIG; Santa Casa da Misericórdia de Ouro Preto; Santa Casa de Caridade de Diamantina; Sociedade Brasileira de Amparo a Saúde (SOBRASA); Unidade de Emergência do Hospital das Clínicas da FMRP-USP; Irmandade Santa Casa de Misericórdia de Porto Alegre:; Hospital de Clínicas da Universidade Estadual de Campinas (UNICAMP); Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP); Hospital São Paulo da Universidade Federal de São Paulo (UNIFESP); Vila Velha Hospital. **Colombia:** Organización Latinoamericana para el Fomento de la Investigación en Salud (OLFIS), Bucaramanga, Colombia; Clinica Chicamocha; Fundación Valle del Lili - Universidad ICESI; Fundación Cardiovascular de Colombia; Hospital Pablo Tóbon Uribe; Hospital Santa Clara; Hospital Universitario del Valle. **Italy:** Policlinico Paolo Giaccone. University of Palermo. **Malaysia:** University Malaya Medical Centre. Poland: Jagiellonian University Medical College. **Portugal:** Hospital de São Francisco Xavier, Centro Hospitalar de Lisboa Ocidental. **Spain:** Hospital Clinico Universitario. University of Valencia**. Uruguai:** Hospital Español.

Informed consent was obtained from all patients´ representatives.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

ABC: Grants from Bactiguard, Ionis Pharmaceuticals, Brazilian Ministry of Health (PROADI-SUS), Brazilian Ministry of Science and Technology, Bayer, Pfizer, Hillrom, Fisher & Paykel, Baxter; VCV: Grants from

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Authors' contributions

ABC, KB and VCV conceptualized the study, wrote the protocol, and drafted the manuscript.

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CONFLICT OF INTEREST

ABC: Grants from Bactiguard, Ionis Pharmaceuticals, Brazilian Ministry of Health (PROADI-SUS), Brazilian Ministry of Science and Technology, Bayer, Pfizer, Hillrom, Fisher & Paykel, Baxter; VCV: Grants from Aspen.

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