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Artigo original

Factors associated with sepsis and conditions that predict death for elderly people with respiratory diseases*

Fatores associados à sepse e condições preditoras de óbito para pessoas idosas com doenças respiratórias

Factores asociados a la sepsis y condiciones que predicen la muerte de ancianos con enfermedades respiratorias

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Abstract

Objective: to analyze the factors associated with sepsis, as well as the conditions that predict death in elderly people admitted to Intensive Care Units, with an initial diagnosis of acute respiratory diseases not related to health care. **Methodology:** mixed cohort epidemiological study, carried out between September 2019 and September 2020. Data were collected from electronic medical charts and associations were checked in bivariate analysis and logistic regression. **Results:** of the studied 228 elderly people, 125 (54.5%) passed away and 204 (89.5%) had sepsis. Urinary invasive devices (RR=1.754; 95% CI 1.360-2.263), presence of sepsis based on the Sepsis-3 consensus (RR=3.55; 95% CI 1.23-10.27) and Covid-19 (RR=1. 39; 95% CI 1.08-1.78) were predictors for death. **Conclusion:** the factors associated with sepsis among patients with Covid-19 and other respiratory infections are different. The conditions that predict death for elderly people with acute respiratory infections not related to health care were: sepsis, Covid-19 and urinary invasive device.
Descriptors: Death; Aged; Sepsis; Respiratory Tract Infections; Covid-19

Resumo

Objetivo: analisar os fatores associados à sepse, bem como as condições preditoras do óbito em pessoas idosas, internadas em Unidade de Terapia Intensiva, com diagnóstico inicial de doenças respiratórias

agudas não relacionadas à assistência à saúde. **Método:** estudo epidemiológico de coorte mista, realizado entre setembro de 2019 e setembro de 2020. Os dados foram coletados nos prontuários eletrônicos e verificada associação em análise bivariada e regressão logística. **Resultados:** das 228 pessoas idosas estudadas, 125 (54,5%) faleceram e observaram-se 204 (89,5%) com sepse. Dispositivos invasivos urinários (RR=1,754; IC 95% 1,360-2,263), presença de sepse segundo o consenso Sepsis-3 (RR=3,55; IC 95% 1,23-10,27) e Covid-19 (RR=1,39; IC 95% 1,08-1,78) foram preditores para o óbito. **Conclusão:** os fatores associados à sepse entre pacientes de Covid-19 e de outras infecções respiratórias são diferentes. As condições preditoras do óbito para pessoas idosas com infecções respiratórias agudas não relacionadas à assistência à saúde foram: sepse, Covid-19 e dispositivo invasivo urinário.
Descritores: Morte; Idoso; Sepse; Infecções Respiratórias; Covid-19

Resumen

Objetivo: analizar los factores asociados a la sepsis, así como las condiciones que predicen la muerte de ancianos ingresados en una Unidad de Cuidados Intensivos, con diagnóstico inicial de enfermedades respiratorias agudas no relacionadas con la asistencia sanitaria. **Metodología:** estudio epidemiológico de cohorte mixta, realizado entre septiembre de 2019 y septiembre de 2020. Los datos se recolectaron de historias clínicas electrónicas y se verificaron asociaciones en análisis bivariado y regresión logística. **Resultados:** de los 228 ancianos estudiados, 125 (54,5%) fallecieron y 204 (89,5%) presentaron sepsis. Dispositivos urinarios invasivos (RR=1,754; IC 95% 1,360-2,263), presencia de sepsis según el consenso Sepsis-3 (RR=3,55; IC 95% 1,23-10,27) y Covid-19 (RR=1,39; 95 %IC 1,08-1,78) fueron predictores de muerte. **Conclusión:** los factores asociados a la sepsis entre pacientes con Covid-19 y otras infecciones respiratorias son diferentes. Las condiciones que predicen la muerte de ancianos con infecciones respiratorias agudas no relacionadas con la asistencia sanitaria fueron: sepsis, Covid-19 y dispositivo urinario invasivo.
Descriptores: Muerte; Anciano; Sepsis; Infecciones del Sistema Respiratorio; Covid-19

Introduction

Changes during the aging process, such as lung stiffness, reduced ciliary activity and decreased immunological efficiency, favor the occurrence of respiratory diseases and their respective complications among elderly people. These diseases promote an increase in hospitalization of elderly citizens, including in Intensive Care Units (ICUs).[1]

Acute respiratory diseases not associated with health care include inflammatory processes across a broad spectrum of events, with different etiologies and different severities, always undermining the respiratory tract. According to their anatomical location, they can be classified in the upper or lower airways, involving pharyngitis, tonsillitis, sinusitis, bronchitis, bronchiolitis and pneumonia.[2]

Acute respiratory diseases are responsible for more than 4 million deaths every year, being the main cause of death in developing countries, and also the main cause of death from infection around the world.[3] Infection is an independent predictor of mortality from sepsis,

where respiratory infections are among those most commonly associated with this mortality.[4]

Sepsis is a multifactorial condition with a generalized systemic response with organ failure in the presence of an infection.[5-6] In 2017, it was estimated that 11 million deaths related to sepsis would occur worldwide, representing 19.7% of total deaths.[7] Data from the Latin American Sepsis Institute (ILAS, as per its Portuguese acronym) indicate that, in Brazil, 30% of ICU beds are occupied by patients with sepsis, with a fatality rate of 55%.[8-9]

Studies carried out in Denmark and Spain observed that respiratory diseases had a numerical reduction compared to periods before the pandemic, but mortality rates were higher for conditions such as pneumonia and sepsis.[10-11] Data analysis is essential for understanding the various aspects that permeate hospital admissions, with special attention to the most vulnerable populations, such as the elderly citizens, in order to define public policies focused on monitoring and caring for these populations.

Therefore, respiratory diseases not related to health care are important causes of illness, with the potential to reduce quality of life, hospitalizations and deaths. There is a need to understand whether cases of respiratory diseases in elderly people progress to sepsis and death, and whether sociodemographic and health factors are associated with the prognosis.

In view of the foregoing, the objective of this study was to analyze the factors associated with sepsis, as well as the predictive conditions for the death of elderly people admitted to ICUs, with an initial diagnosis of acute respiratory disease not related to health care.

Methodology

This is an epidemiological, descriptive and analytical research, typified as a hospital-based mixed cohort, carried out in a medium-sized public teaching hospital, located in the South Region of Brazil, held between the months of August 2020 and March 2021.

Cohort is an epidemiological study carried out in a population group that has some characteristic in common, for which the researcher must analyze the relationship between the risk factors and the development of illnesses. At the beginning of this study, the cohort participants did not have the outcome studied over time.[12] The current work is a cohort study, since all individuals were studied because they were elderly citizens and had an infection not related to health care. The observed outcomes were sepsis and death. When entering the hospital, everyone was alive, where the conditions of exposure to sepsis and death upon

admission to the ICU were assessed, and progress and outcomes were monitored throughout hospitalization. At the beginning of data collection, the researchers were present, but part of the patient data were collected retrospectively and part prospectively, thus characterizing the mixed temporality.

During the analyzed period, the institution had 20 regular beds in the general ICU and 30 ICU beds for Covid-19. The ICU beds for Covid-19 were implemented in March 2020 and underwent increasing numerical evolution, until the aforementioned quantity was reached.

The population was composed of all elderly people (≥60 years old), admitted to ICUs and diagnosed with acute respiratory disease not related to health care, between September 2019 and September 2020. Patients with duplicate records or with respiratory disease related to health care.

A semi-structured instrument was developed with the variables of interest for data collection: gender, age, age group, skin color, weight, chronic diseases, acute respiratory diseases, previous continuous medication use, etiological agents, invasive devices, antibiotic use, antiviral use, vasopressor use, vital signs (heart rate and body temperature, among others), laboratory tests (culture, platelets, lactate and C-reactive protein, among others), sepsis based on the Sepsis-3 consensus criteria, sepsis diagnosis in medical charts, septic shock, Sequential Organ Failure Assessment (SOFA) and Quick Sequential Organ Failure Assessment (qSOFA) scores, in addition to the outcome (discharge, transfer or death).

The data available in the electronic medical charts of the Health Care Management System of the Brazilian Unified Health System (GSUS, as per its Portuguese acronym) were collected. A monthly search of ICU admissions was carried out and all records that revealed primary codes from the International Statistical Classification of Diseases and Related Health Problems, in the 10th Revision (ICD-10) related to the respiratory system or other septicemias were selected. The ICD-10 hospitalization code referring to "other septicemias" was observed to check whether the origin of the sepsis was related to a respiratory infection not related to health care. Based on all patients selected using the ICD-10 primary diagnostic criteria, health care-associated infections (HAIs) were excluded, consulted in a list made available by the Center for Epidemiology and Hospital Infection Control (NUCIH, as per its Portuguese acronym), as well as duplicate records. With the remaining medical charts, those that corresponded to acute respiratory diseases not related to health care were confirmed. Before each data collection

from the selected individuals, the diagnosis of acute respiratory diseases was confirmed again, through the signs, symptoms and descriptions observed in the medical charts.

Of the 1,473 ICU admissions during the study period, 893 (60.6%) involved elderly people and 296 were elderly people who had an ICD-10 code for hospitalization related to the respiratory system or other septicemias. Of these, 6 were excluded due to HAIs, 17 had duplication in the system and 44 did not have an acute respiratory disease, leaving 229 elderly people. Nonetheless, one of them was excluded from the study because he clinically differed from the others (the only patient who had sepsis criteria after the first 24 hours of admission to the ICU), and then the study population was composed of 228 elderly people.

A pilot collection was carried out with three medical charts, in order to check the applicability of the research instrument. Furthermore, the first 20 medical charts had their data collected twice, with a view to observing the coherence of the information between both researchers who collected the information.

The data were organized in a Microsoft Excel® spreadsheet and subsequently analyzed using the Statistical Package for the Social Sciences – SPSS®, version 22. Categorical variables were expressed in simple and relative frequencies, WHILE continuous variables were summarized by mean and standard deviation, or median and interquartile range, according to the distribution pattern. In order to test the normality of the variables, the Shapiro-Wilk and Kolmogorov-Smirnov tests were employed, according to the amount of information available on each tested variable. The association between exposure and outcome variables was assessed using the Chi-square statistical test, as well as the relative risk association measure, when dealing with categorical variables. For numerical variables, Student's t-test and Mann-Whitney U test were used. Results with a p-value <0.05 were considered statistically significant.

In bivariate analysis, it was decided to introduce the risks of death according to the presence of acute respiratory diseases due to Covid-19 and other infections separately, due to the high frequency and specificities of this new condition, still to be clarified in detail, and visualization of its influence on the outcome of death. However, the construction of the predictive model, in multivariate analysis, considered the set of all acute respiratory diseases not related to health care, responding to the general objective of the study.

Multiple logistic regression models were created with the stepwise backward method, proceeding from the simplest to the most complex. In order to enter the variables into the

regression models, p<0.20 was used, where the adjustment of the models was checked using the Akaike Information Criterion (AIC) and p<0.05. Interactions between the independent variables of the final model were tested using the Chi-square test, and the final regression model was introduced with adjusted relative risk and p-value. Regression analyses were performed using RStudio Cloud software.

This work is in accordance with Resolutions nº 466/2012, nº 510/2016 and nº 580/2018, being part of a research called "Studies on health surveillance, mortality and hospital epidemiology", approved by the Research Ethics Committee of the State University of Ponta Grossa, according to opinions nº 4,110,879, dated June 25, 2020, and nº 4,650,824, dated April 14, 2021, through the Certificate of Presentation for Ethical Consideration nº 33550920900000105.

Results

Of the 228 elderly people with acute respiratory diseases not related to health care, 51.8% were male, 78.5% were aged between 60 and 79 years, 86.4% were white and 89.0% had chronic diseases. The virus was the most common etiological agent, found in 64.0% of patients, the majority of which were SARS-CoV-2 (63.6%). The second most frequently diagnosed microorganism was the bacterium Staphylococcus aureus (4.8%). All elderly patients were using some invasive device, 53.5% of participants were using up to three invasive devices and 79.8% were taking prescribed antibiotics (Table 1).

Of the identified respiratory infections, the most common was Covid-19 (63.6%), followed by pneumonia (34.2%), flu (1.3%) and bronchitis (0.9%). Regarding the sepsis diagnosis, it was found that 34.6% had a diagnosis of sepsis recorded in the medical chart, but 89.5% had sepsis based on the Sepsis-3 consensus criteria (Table 1).

Table 1 – Sociodemographic and clinical characteristics of elderly people admitted to Intensive Care Units with an initial diagnosis of acute respiratory diseases not related to health care. Ponta Grossa, Paraná, Brazil, 2021 (n=228).

Variable		N (%)
Gender	Male	118 (51.8)
	Female	110 (48.2)
Age group	60 to 79 years	179 (78.5)
	Equal to or greater than 80	49 (21.5)

	years old	
Skin color	Others (browns, blacks)	31 (13.6)
	White	197 (86.4)
Presence of chronic diseases	No	25 (11.0)
	Yes	203 (89.0)
Etiological agent	Bacteria	22 (9.6)
	Virus	146 (64.0)
	Fungus	2 (0.9)
	Mixed	8 (3.5)
	Not identified	50 (21.9)
Number of invasive devices	Up to 3	192 (84.2)
	4 or more	36 (15.8)
Antibiotic use	No	46 (20.2)
	Yes	182 (79.8)
Acute respiratory diseases	Covid-19	145 (63.6)
	Pneumonia	78 (34.2)
	Flu	3 (1.3)
	Bronchitis	2 (0.9)
Sepsis recorded in medical charts	Yes	79 (34.6)
	No	149 (65.4)
Sepsis based on the Sepsis-3 consensus criteria	Yes	204 (88.5)
	No	24 (11.5)

Factors associated with the presence of sepsis

Of the 204 elderly patients with sepsis, 65.7% had acute respiratory diseases not related to health care due to Covid-19 and 34.3% had acute respiratory diseases not related to health care due to other infections. The risk for sepsis in the presence of acute respiratory disease not related to health care due to Covid-19 was higher in elderly patients with chronic neurological disease (RR=1.17; p=0.045), with a nutritional invasive device (RR=1.25; p<0.001), with urinary invasive device (RR=1.26; p<0.001), with four or more invasive devices (RR=1.17; p=0.026), with antibiotic use (RR=1 .21; p=0.007), with antiviral use (RR=1.18; p=0.007), with vasopressor use (RR=1.24; p<0.001), with a diagnosis of sepsis in the medical chart (RR=1.14; p=0.036), with septic shock (RR=1.17; p=0.045) and outcome of death (RR=1.33; p<0.001) (Table 2).

Meanwhile, in patients with acute respiratory diseases not related to health care due to other infections, the risk for the presence of sepsis was higher in elderly people using a nutritional invasive device (RR=1.20; p=0.008), with urinary invasive device (RR=1.17; p=0.014) and antibiotic use (RR=1.59; p=0.033) (Table 2).

Predictors of deaths

Among the 228 participants, 54.8% passed away and 45.2% were discharged. Of the 125 deaths, 71.2% had confirmed acute respiratory diseases not related to health care due to Covid-19 and 28.8% had acute respiratory diseases not related to health care due to other infections. Regarding deaths in elderly people with Covid-19, there was a predominance of men (56.2%), aged between 60 and 79 years (79.8%), whites (84.3%), with chronic diseases (86.5%) – mainly chronic cardiovascular diseases (71.9%), previously using continuous medication (84.3%), using up to three invasive devices (75.3%) – mainly circulatory devices (98.9%), using antibiotics (76.4%), without a diagnosis of sepsis in the medical chart (52.8%), with sepsis based on the Sepsis-3 consensus (97.8%) and without shock septic (75.3%) (Tables 2 and 3).

In the group of patients who died and had acute respiratory diseases not related to health care due to other infections, it was observed that the majority were men (52.8%), aged between 60 and 79 years (66.7%), whites (88.9%), with chronic diseases (86.1%) – mainly chronic cardiovascular diseases (66.7%), with previous continuous medication use (77.8%), without treatment prior to hospitalization (66.7%), using up to three invasive devices (83.3%) – mainly circulatory and respiratory devices (97.2%), with antibiotic use (97.2%), with negative culture (61.1%), vasopressor use (63.9%), without a diagnosis of sepsis in the medical chart (58.3%), with sepsis based on the Sepsis-3 consensus (97.8%) and without septic shock (58.3%) (Tables 2 and 3).

The risk of death in the presence of Covid-19 was higher in elderly people with a nutritional invasive device (RR=2.04; p<0.001), with a urinary invasive device (RR=2.32; p<0.001), with four or more invasive devices (RR=1.53; p=0.007), with vasopressor use (RR=1.80; p<0.001), with sepsis based on the Sepsis-3 consensus (RR=6.16; p<0.001), with a diagnosis of sepsis in the medical chart (RR=1.89; p<0.001) and with septic shock (RR=1.76; p<0.001). Meanwhile, in patients with other respiratory infections, the risk of death was higher in elderly people with a positive culture (RR=1.63; p=0.044) and using vasopressors (RR=1.91; p=0.008) (Tables 2 and 3).

Table 2 – Bivariate analysis of factors associated with the death of elderly people admitted to Intensive Care Units with an initial diagnosis of acute respiratory diseases not related to health care. Ponta Grossa, Paraná, Brazil, 2021 (n=228).

Variable	Covid-19			Other respiratory diseases		
	Death n/total (%)	Discharge n/total (%)	RR (95% CI)	Death n/total (%)	Discharge n/total (%)	RR (95% CI)

Gender	Male	50/84 (59.5)	34/84 (40.5)	1,05 (0,80-1.38)	19/34 (55.9)	15/34 (44.1)	1.34 (0.84-2.15)
	Female	39/69 (56.5)	30/69 (43.5)	Ref.	17/41 (41.5)	24/41 (58.5)	Ref.
Age group	≥ 80 years	18/30 (60.0)	12/30 (40.0)	1.03 (0,74-1.44)	12/19 (63.2)	7/19 (36.8)	1.47 (0.93-2.32)
	60 to 79 years	71/123 (57.7)	52/123 (42.3)	Ref.	24/56 (42.9)	32/56 (57.1)	Ref.
Skin color	Others	14/22 (63.6)	8/22 (36.4)	1.11 (0.78-1,57)	4/9 (44.4)	5/9 (55.6)	0.91 (0.42-1.98)
	White	75/131 (57.3)	56/131 (42.7)	Ref.	32/66 (48.5)	34/66 (51.5)	Ref.
Presence of chronic diseases	Yes	77/135 (57.0)	58/135 (43.0)	0.85 (0.59-1.22)	31/68 (45.6)	37/68 (54.4)	0.63 (0.37-1.09)
	No	12/18 (66.7)	6/18 (33.3)	Ref.	5/7 (71.4)	2/7 (28.6)	Ref.
Dyslipidemia	Yes	6/10 (60.0)	4/10 (40.0)	1.03 (0.61-1.74)	0/2 (0.0)	2/2 (100.0)	NA
	No	83/143 (58.0)	60/143 (42.0)	Ref.	36/73 (49.3)	37/73 (50.7)	Ref.
Chronic renal disease	Yes	2/4 (50.0)	2/4 (50.0)	0.85, (0.31-2.30)	1/1 (100.0)	0/1 (0.0)	2.11 (1.66-2.68)
	No	87/149 (58.4)	62/149 (41.6)	Ref.	35/74 (47.3)	39/74 (52.7)	Ref.
Chronic endocrine disease	Yes	9/22 (40.9)	13/22 (59.1)	0.67 (0.39-1.12)	2/3 (66.7)	1/3 (33.3)	1.41 (0.61-3.25)
	No	80/131 (61.1)	51/131 (38.9)	Ref.	34/72 (47.2)	38/72 (52.8)	Ref.
Chronic neurological disease	Yes	18/26 (69.2)	8/26 (30.8)	1.23 (0.91-1.67)	6/16 (37.5)	10/16 (62.5)	0.73 (0.37-1.45)
	No	71/127 (55.9)	56/127 (44.1)	Ref.	30/59 (50.8)	29/59 (49.2)	Ref.
Chronic immunological disease	Yes	1/3 (33.3)	2/3 (66.7)	0.56 (0.11-2.83)	0/1 (0.0)	1/1 (100.0)	NA
	No	88/150 (58.7)	62/150 (41.3)	Ref.	36/74 (48.6)	38/74 (51.4)	Ref.
Obesity	Yes	1/5 (20.0)	4/5 (80.0)	0.33 (0.05-1.95)	1/1 (100.0)	0/1 (0.0)	2.11 (1.66-2.68)
	No	88/148 (59.5)	60/148 (40.5)	Ref.	35/74 (47.3)	39/74 (52.7)	Ref.
Chronic respiratory disease	Yes	20/31 (64.5)	11/31 (35.5)	1.14 (0.84-1.54)	16/35 (45.7)	19/35 (54.3)	0.91 (0.56-1.47)
	No	69/122 (56.6)	53/122 (43.4)	Ref.	20/40 (50.0)	20/40 (50.0)	Ref.
Neoplasm	Yes	3/4 (75.0)	1/4 (25.0)	1.29 (0.72-2.32)	1/2 (50.0)	1/2 (50.0)	1.04 (0.25-4.25)
	No	86/149 (57,7)	63/149 (42,3)	Ref.	35/73 (47,9)	38/73 (52,1)	Ref.

Diabetes Mellitus	Yes	31/53 (58.5)	22/53 (41.5)	1.00 (0.76-1.33)	10/24 (41.7)	14/24 (58.3)	0.81 (0.47-1.40)
	No	58/100 (58.0)	42/100 (42.0)	Ref.	26/51 (51.0)	25/51 (49.0)	Ref.
Chronic cardiovascular disease	Yes	64/114 (56,1)	50/114 (43,9)	0,87 (0,65-1,16)	24/53 (45,3)	29/53 (54,7)	0,83 (0,51-1,34)
	No	25/39 (64.1)	14/39 (35.9)	Ref.	12/22 (54.5)	10/22 (45.5)	Ref.
Previous continuous medication use	Yes	75/131 (57.3)	56/131 (42.7)	0,90 (0,63-1.27)	28/61 (45.9)	33/61 (54.1)	0,80 (0,47-1.36)
	No	14/22 (63.6)	8/22 (36.4)	Ref.	8/14 (57.1)	6/14 (42.9)	Ref.
Etiological agent	Virus	83/145 (57.2)	62/145 (42.8)	0.76 (0.49-1.16)	0/1 (0.0)	1/1 (100.0)	NA
	Bacteria, fungus, mixed	6/8 (75.0)	2/8 (25.0)	Ref.	14/24 (58.3)	10/24 (41.7)	Ref.

Table 3 – Bivariate analysis of factors associated with the death of elderly people admitted to Intensive Care Units with an initial diagnosis of acute respiratory diseases not related to health care. Ponta Grossa, Paraná, Brazil, 2021 (n=228).

Variable		Covid-19			Other respiratory diseases		
		Death n/total (%)	Discharge n/total (%)	RR (95% CI)	Death n/total (%)	Discharge n/total (%)	RR (95% CI)
Drainage invasive device	Yes	5/5 (100.0)	0/5 (0.0)	1.76 (1,53-2.02)	2/4 (50.0)	2/4 (50.0)	1.04 (0,38-2.86)
	No	84/148 (56.8)	64/148 (43.2)	Ref.	34/71 (47.9)	37/71 (52.1)	Ref.
Nutritional invasive device	Yes	60/77 (77.9)	17/77 (22.1)	2.04 (1.49-2.78)	24/45 (53.3)	21/45 (46.7)	1.33 (0.79-2.23)
	No	29/76 (38.2)	47/76 (61.8)	Ref.	12/30 (40.0)	18/30 (60.0)	Ref.
Respiratory invasive device	Yes	86/146 (58.9)	60/146 (41.1)	1.37 (0,57-3.26)	35/71 (49.3)	36/71 (50.7)	1.97 (0.35-10.94)
	No	3/7 (42.9)	4/7 (57.1)	Ref.	1/4 (25.0)	3/4 (75.0)	Ref.
Circulatory invasive device	Yes	88/151 (58.3)	63/151 (41.7)	1.16 (0.29-4.69)	35/74 (47.3)	39/74 (52.7)	0.47 (0.37-0.60)
	No	1/2 (50.0)	1/2 (50.0)	Ref.	1/1 (100.0)	0/1 (0.0)	Ref.
Urinary invasive device	Yes	60/72 (83.3)	12/72 (16.7)	2.32 (1.70-3.17)	23/42 (54.8)	19/42 (45.2)	1.39 (0.83-2.30)
	No	29/81 (35.8)	52/81 (64.2)	Ref.	13/33 (39.4)	20/33 (60.6)	Ref.

Number of invasive devices	4 ou more	22/27 (81.5)	5/27 (18.5)	1.53 (1.20-1.95)	6/9 (66.7)	3/9 (33.3)	1.46 (0.86-2.49)
	Up to 3	67/126 (53.2)	59/126 (46.8)	Ref.	30/66 (45.5)	36/66 (54.5)	Ref.
Antibiotic use	Yes	68/112 (60.7)	44/112 (39.3)	1.18 (0.84-1.65)	33/70 (47.1)	37/70 (52.9)	0.78 (0.36-1.67)
	No	21/41 (51.2)	20/41 (48.8)	Ref.	3/5 (60.0)	2/5 (40.0)	Ref.
Antiviral use	Yes	25/49 (51.0)	24/49 (49.0)	0.82 (0.60-1.13)	9/19 (47.4)	10/19 (52.6)	0.98 (0.56-1.69)
	No	64/104 (61.5)	40/104 (38.5)	Ref.	27/56 (48.2)	29/56 (51.8)	Ref.
Culture	Positive	7/10 (70.0)	3/10 (30.0)	1.22 (0.79-1.87)	14/21 (66.7)	7/21 (33.3)	1.63 (1.05-2.54)
	Negative	82/143 (57.3)	61/143 (42.7)	Ref.	22/54 (40.7)	32/54 (59.3)	Ref.
Vasopressor use	Yes	46/57 (80.7)	11/57 (19.3)	1.80 (1.39-2.32)	23/36 (63.9)	13/36 (36.1)	1.91 (1.15-3.18)
	No	43/96 (44.8)	53/96 (55.2)	Ref.	13/39 (33.3)	26/39 (66.7)	Ref.
Sepsis based on the Sepsis-3 consensus criteria	Yes	87/134 (64.9)	47/134 (35.9)	6.16 (1.65-23.01)	35/70 (50.0)	35/70 (50.0)	2.5 (0.42-14.65)
	No	2/19 (10.5)	17/19 (89.5)	Ref.	1/5 (20.0)	4/5 (80.0)	Ref.
Sepsis diagnosis recorded in medical charts	Yes	42/49 (85.7)	7/49 (14.3)	1.89 (1.49-2.41)	15/30 (50.0)	15/30 (50.0)	1.07 (0.66-1.72)
	No	47/104 (45.2)	57/104 (54.8)	Ref.	21/45 (46.7)	24/45 (53.3)	Ref.
Septic shock	Yes	22/24 (91.7)	2/24 (8.3)	1.76 (1.43-2.16)	15/29 (51.7)	14/29 (48.3)	1.13 (0.70-1.81)
	No	67/129 (51.9)	62/129 (48.1)	Ref.	21/46 (45.7)	25/46 (54.3)	Ref.

In elderly people who passed away and had acute respiratory diseases not related to health care due to Covid-19, it was also observed that the median age was 73 years, the weight was 74.0 kilograms (kg), with total length of stay of 8 days, PaO_2/FiO_2 ratio of 176.6 mmHg, platelets at 188,0x10^3 mm^3, bilirubin at 0.6 mg/dl, mean arterial pressure at 87 mmHg, Glasgow at 11 points, creatinine at 1.4 mg/dl, heart rate at 98.0 beats per minute (bpm), temperature at 36.0ºC, respiratory rate at 22 breaths per minute (bpm), leukocytes at 12,1 x10^3 mm^3, saturation

at 92%, lactate at 14.1 mg/dl, systolic blood pressure at 120 mmHg, C-reactive protein at 18.1 md/dl, SOFA score at 8 points and qSOFA score at 1 point.

In patients who passed away and had acute respiratory diseases not related to health care due to other infections, the medians corresponded to 75 years, the weight was 65.0 kg, the total length of hospital stay was 9 days, the PaO_2/FiO_2 ratio was 222.7 mmHg, platelets at 229,0x10^3 mm^3, bilirubin at 0.6 mg/dl, mean arterial pressure at 81 mmHg, Glasgow at 7.0 points, creatinine at 1.4 mg/dl, heart rate at 96.0 bpm, temperature at 36.1ºC, respiratory rate at 18 bpm, leukocytes at 14,8 x10^3 mm^3, saturation at 95%, lactate at 17.8 mg/dl, systolic blood pressure at 115.0 mmHg, C-reactive protein at 7.8 md/dl, SOFA score at 8 points and qSOFA score at 1 point.

The indexes of total length of stay (p=0.035), the PaO_2/FiO_2 ratio (p=0.017), platelets (p<0.001), mean arterial pressure (p=0.030), Glasgow score (p<0.001), creatinine (p<0.001), temperature (p=0.050), leukocytes (p=0.031), saturation (p=0.044), SOFA score (p<0.001) and qSOFA score (p<0.001) revealed association with death in elderly people with acute respiratory diseases not related to health care due to Covid-19. Meanwhile, mean arterial pressure (p=0.041), systolic blood pressure (p=0.023) and SOFA score (p=0.044) were associated with death in elderly people with acute respiratory diseases not related to health care due to other infections.

In a multivariate analysis, it was noted that the risk factors that predicted the death of elderly people admitted to ICUs with an initial diagnosis of acute respiratory diseases not related to health care involved urinary invasive devices, sepsis based on the Sepsis-3 consensus and Covid-19 (Table 4). Regardless of other conditions, elderly people with sepsis had three times the risk of death compared to those without sepsis. The urinary invasive device increased the risk of dying by approximately two times, and Covid-19 increased the probability of dying by 40%.

Table 4 – Predictive conditions* of deaths in elderly people admitted to Intensive Care Units with an initial diagnosis of acute respiratory diseases not related to health care. Ponta Grossa, Paraná, Brazil, 2021 (n=228).

Variable	Relative Risk (95% CI†)	p-value
Urinary invasive device	1.754 (1.360-2.263)	<0.001
Sepsis based on the Sepsis-3 consensus	3.555 (1.230-10.273)	0.019
Covid-19	1.391 (1.086-1.781)	0.008

*Interactions between the independent variables of the final model were tested. It was noted that the variables – urinary invasive device and sepsis were statistically associated (p-value<0,001). The interaction was included in the multiple-model approach and was not significant. Therefore, the introduced model contains the variables without the interactions. †CI: Confidence Interval.

Discussion

The main findings of the current study show a high incidence of sepsis and deaths in elderly people admitted to ICUs with an initial diagnosis of acute respiratory diseases not related to health care. Some risk factors were common to patients with Covid-19 and those with other infections, such as nutritional and urinary invasive devices and antibiotic use.

Sepsis in elderly people with acute respiratory diseases not related to health care due to Covid-19 was associated with chronic neurological diseases and total length of stay. In the subpopulation with acute respiratory diseases due to other respiratory infections, sepsis was associated with the patient's age and weight. The use of urinary invasive devices, sepsis based on the Sepsis-3 consensus and covid-19 were independent predictors of deaths.

One of the main causes of hospitalization of elderly people in ICUs was respiratory system infections and their complications, according to a multicenter prospective cohort held in hospitals in the South Region of Brazil.[13] The prevalence of Covid-19 characterizes the impact that the pandemic has provoked on all aspects of global health. Pneumonia can be explained by physiological changes linked to aging and a decrease in the immune response. It is underlined that prevention for both conditions and other community-acquired respiratory infections begins with awareness-raising actions and changes in the population's lifestyle.

The high incidence of sepsis characterized in elderly people, with respiratory infections and in ICUs, conditions that disproportionately affect its frequency, corroborates retrospective exploratory research held in a Brazilian ICU, where, of the total of 1,557 analyzed medical charts, 71.4% were classified as with sepsis.[14] Another secondary analysis of audit data from the Intensive Care Over Nations showed that, of the 10,012 studied patients, a total of 2,963 had sepsis (29.6%).[15] The difference in results is highlighted by the World Health Organization in the first global report on sepsis, showing inequality between countries, the use of different definitions of sepsis and the need for better data, through strengthening information systems, access to diagnostic and care-related tools, in order to achieve a true understanding of this

condition.[16]

Some of the biological changes expected in the elderly person as a result of aging occur in the immune system, such as the thymic involution, which depresses the function of T cells; the decrease in cytokines; and the altered expression and function of toll-like receptors and B cells, with production of low-affinity antibodies, resulting in immunosenescence, that is, the functional decline of the immune system with aging, thus predisposing to the risk of developing infections and sepsis with more complex and prolonged cases.[17] This would be a possible justification for the association of sepsis with age in other acute respiratory infections not related to health care.

With the demographic transition and increasing population aging, the frequency of deaths is expected to be higher among elderly citizens. Nonetheless, mortality may also be related to senility, delays in terms of seeking care and the high transmissibility of respiratory infections, thus reinforcing the need to implement health interventions of public interest, such as access to vaccination and primary health care.[18] The high mortality noted in the current research due to acute respiratory infections not related to health care corroborates a retrospective observational study in the South Region of Brazil that assessed mortality in the elderly population. Of the 80,170 deaths that occurred between 2009 and 2018, 42.2% were due to community-acquired pneumonia. Of these, 83.9% occurred in the elderly population, and 83.8% of deaths in the elderly patients occurred in the hospital setting.[19]

Regarding the increased risk of death in elderly people with urinary invasive devices, their use may represent the process of organic dysfunction from sepsis until the clinical picture of renal failure prior to death, predisposing to new infections, in addition to being a constant element in the care-related protocol for patients with acute respiratory diseases not related to health care due to Covid-19, who make up the majority in this study, in order to facilitate the pronation process. Furthermore, the using time of invasive devices contributes significantly to the clinical outcome of patients. Retrospective cross-sectional research, carried out with elderly people admitted to ICUs in the Northeast Region of Brazil, recorded the association between the use of an indwelling bladder catheter and the outcome of death ($p<0.001$).[20]

Related to the higher risk of death in elderly people with sepsis based on the Sepsis-3 consensus, the mortality of patients with sepsis in the ICU setting exceeds that of non-septic patients, and elderly people die significantly more from sepsis than non-elderly people.[21] A

series of factors, such as immune function, comorbidities and length of stay, can influence the unfavorable outcome. The body's reactions to infections may be attenuated in elderly people, causing difficulty in terms of differential diagnosis.[22] The effective implementation of managed care-related protocols can lead to the evolution of sepsis to favorable prognoses for survival.[4]

When the health team recognizes sepsis and the diagnosis is mentioned in the medical chart, it may be that the patients are clinically in a more serious situation and, therefore, the risk is increased, as introduced in this study, in the bivariate analysis. Apparently, milder conditions may be undergoing clinical diagnosis and being recognized as sepsis late. Accordingly, training and monitoring actions are very effective in terms of improving this condition.[23]

Viral infection was the main cause of sepsis, as up to 42% of patients with sepsis may be negative culture, thus suggesting a non-bacterial cause.[24] In the current research, sepsis in elderly people with Covid-19 increased the risk of death by up to six times, an association that remained in the multivariate analysis, reducing its effect, but remaining high for all patients with respiratory infection. It is emphasized that, due to the pandemic situation, care for Covid-19 respiratory infection may have been provided by teams that had members who were inexperienced in intensive care or who were exhausted and perhaps unaware of the relationship between covid-19 and sepsis.

Although current understanding of the pathophysiology of sepsis has improved, the differences between viral and bacterial sepsis in terms of pathophysiology are not well understood.[25] In some cases, viral sepsis is considered to be direct cellular damage induced by viruses rather than systemic dysregulation caused by the virus.[26]

An early approach to sepsis, within the first hour, is essential for reducing mortality. The latest update of the Surviving Sepsis Campaign recommends checking the serum lactate level within one hour, in order to assess perfusion status, collecting cultures before starting antimicrobial therapy, administering broad-spectrum antibiotics intravenously, performing volume replacement in patients with hypotension or lactate twice above the reference value and using vasopressors during or after volume replacement, with a view to maintaining mean arterial pressure above 65 mmHg, with monitoring of progress.[27]

In Brazil and around the world, the distribution of cases and deaths from Covid-19, according to age group, reveals a higher incidence in adults, with higher fatality rate in elderly citizens.[28] The lower expression of type 2 angiotensin-converting enzyme (ACE2), induced by

aging, may lead to more severe conditions in patients infected with SARS-CoV-2, due to the exacerbation of the effects mediated by type 2 angiotensin.[29] A survey carried out in China, the first epicenter of the pandemic, revealed the prevalence of elderly people admitted to ICUs, showing a greater probability of progressing to severe forms of the disease, a fact consistent with the increased risk of death as a result of Covid-19 infections revealed in the current study.[28]

The prominence of Covid-19 among other infections may be linked to the absence of specific medicines and vaccines and, even when individuals are immunized, vaccine effectiveness in the elderly patients regresses over time, pointing to the need to maintain non-pharmacological prevention and protection against this infection.

Recognized as a good predictor of ICU mortality, the SOFA score revealed high medians in this study for all patients. Exposure factors, such as mean arterial pressure, creatinine, Glasgow and others, were associated with death in bivariate analysis. As they are components of the SOFA criteria, the findings confirm that death was impacted by the presence of sepsis and Covid-19, as noted in the multivariate model.[30]

When reflecting that many elderly people had, together, the three independent predictive conditions for death, it is noted the severity of the patients and the need for early and immediate interventions that permeate self-care, family involvement, state and municipal management planning and still an assistance bond, with scientifically based care.

Perhaps the differences between patients diagnosed with acute respiratory diseases not related to health care due to Covid-19 and other infections were due to the inequality in the number of cases observed during the study period and analyzed statistically.

In the current perspective of aging, it is crucial to incorporate actions focused on elderly people's needs, providing them with quality of life, autonomy and independence. It should be remembered that decision-making should not be based exclusively on chronological age, but one should take into account the particularities that exist. It means exploring elements associated with mortality from preventable causes, such as community-acquired respiratory infections, can help to develop public policies that strengthen care-related sectors.

The factors associated with sepsis and the predictors for deaths in elderly people highlighted in this study require prevention and protection, in order to reduce potentially avoidable deaths. Knowing, preventing and communicating on the most frequent infections in the territory, understanding how they manifest themselves and also that the outcomes of

sepsis and death may be involved is essential for aging with quality of life for those who are elderly and those who will be in the future.

Regarding limitations, it is mentioned that the non-concurrent study may reveal weaknesses in terms of information bias and the control of confounding variables. Furthermore, the studied cases were all more complex than the population that was not admitted to the ICU setting. Finally, it is added that the studied period may have reduced the effect of bacterial and fungal infections on sepsis and deaths in elderly people.

Nonetheless, this study is unprecedented in the region, since its results add knowledge on the interaction between acute respiratory diseases not related to health care due to Covid-19 and viral sepsis, in addition to their consequences. It also describes the impact of acute respiratory diseases not related to health care on mortality in elderly citizens and contributes to the understanding of the natural history of this group of diseases. In the face of community-acquired respiratory infections, points to be addressed in the health care network for elderly people are revealed. The findings reinforce the importance of communicating to the elderly population, caregivers and organized civil society on the need for immunization.

Conclusion

The risk of sepsis is associated with chronic diseases, invasive devices, the use of medicines and other factors. The factors associated with sepsis among patients with Covid-19 and other respiratory infections are different. Predictive conditions for death in elderly people with acute respiratory infections not related to health care were sepsis, Covid-19 and urinary invasive devices. Furthermore, the incidence of sepsis in elderly people admitted to ICUs for acute respiratory infections not related to health care is high.

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