

The Association Between Bronchoscopy and the Prognoses of Patients With Ventilator-Associated Pneumonia in Intensive Care Units: A Retrospective Study Based on the MIMIC-IV Database

OPEN ACCESS

Edited by:

Xian-Tao Zeng, Wuhan University, China

Reviewed by:

Konlawij Trongtrakul, Chiang Mai University, Thailand Yaolong Chen, Lanzhou University, China Qilin Yang, The Second Affiliated Hospital of Guangzhou Medical University, China

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Specialty section:

This article was submitted to Respiratory Pharmacology, a section of the journal Frontiers in Pharmacology

Received: 03 February 2022 Accepted: 06 May 2022 Published: 08 June 2022

Citation:

Zhang L, Li S, Yuan S, Lu X, Li J, Liu Y, Huang T, Lyu J and Yin H (2022) The Association Between Bronchoscopy and the Prognoses of Patients With Ventilator-Associated Pneumonia in Intensive Care Units: A Retrospective Study Based on the MIMIC-IV Database. Front. Pharmacol. 13:868920. doi: 10.3389/fphar.2022.868920 Luming Zhang^{1,2†}, Shaojin Li^{3,†}, Shiqi Yuan^{4,†}, Xuehao Lu^{1,2}, Jieyao Li¹, Yu Liu¹, Tao Huang², Jun Lyu^{2,5}* and Haiyan Yin¹*

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Background: In intensive care units (ICUs), the morbidity and mortality of ventilatorassociated pneumonia (VAP) are relatively high, and this condition also increases medical expenses for mechanically ventilated patients, which will seriously affect the prognoses of critically ill patients. The purpose of this study was to determine the impact of bronchoscopy on the prognosis of patients with VAP undergoing invasive mechanical ventilation (IMV).

Methods: This was a retrospective study based on patients with VAP from the Medical Information Mart for Intensive Care IV database. The outcomes were ICU and in-hospital mortality. Patients were divided based on whether or not they had undergone bronchoscopy during IMV. Kaplan-Meier (KM) survival curves and Cox proportional-hazards regression models were used to analyze the association between groups and outcomes. Propensity score matching (PSM) and propensity score based inverse probability of treatment weighting (IPTW) were used to further verify the stability of the results. The effect of bronchoscopy on prognosis was further analyzed by causal mediation analysis (CMA).

Results: This study enrolled 1,560 patients with VAP: 1,355 in the no-bronchoscopy group and 205 in the bronchoscopy group. The KM survival curve indicated a significant difference in survival probability between the two groups. The survival probabilities in both the ICU and hospital were significantly higher in the bronchoscopy group than in the no bronchoscopy group. After adjusting all covariates as confounding factors in the Cox model, the HRs (95% CI) for ICU and in-hospital mortality in the bronchoscopy group were 0.33 (0.20–0.55) and 0.40 (0.26–0.60), respectively, indicating that the risks of ICU and in-hospital mortality were 0.67 and 0.60 lower than in the no-bronchoscopy group. The same trend was obtained after using PSM and IPTW. CMA showed that delta-red blood cell

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distribution width (RDW) mediated 8 and 7% of the beneficial effects of bronchoscopy in ICU mortality and in-hospital mortality.

Conclusion: Bronchoscopy during IMV was associated with reducing the risk of ICU and in-hospital mortality in patients with VAP in ICUs, and this beneficial effect was partially mediated by changes in RDW levels.

Keywords: ICU, ventilator-associated pneumonia, bronchoscopy, mortality, causal mediation analysis

INTRODUCTION

Ventilator-associated pneumonia (VAP), defined as infection of the lung parenchyma in patients after at least 48 h of exposure to invasive mechanical ventilation (IMV), (Papazian et al., 2020), is one of the most common infectious diseases in intensive care units (ICUs) (Hunter, 2012), affecting up to 40% of patients on mechanical ventilators (Spalding et al., 2017). Various previous studies found that VAP was associated with longer IMV durations and ICU stays, and also increased antimicrobial use (Hayashi et al., 2013). In some developed countries, VAP was also found to increase the average hospitalization cost of patients by approximately US\$ 40,000 (Zimlichman et al., 2013). The mortality rate of patients with VAP may exceed 50% (Ruiz et al., 2000); the results of 58 randomized studies on VAP indicated that the estimated attributable mortality rate was 9% (range 3-17%) (Melsen et al., 2011). VAP has high morbidity and mortality, and also increases the medical expenses of mechanically ventilated patients, which will seriously affect the prognoses of critically ill patients.

Bronchoscopy has been widely used for clinical diagnoses and treatment of respiratory diseases. Airway examination and transbronchial biopsy have greatly improved the diagnosis rates of pulmonary inflammatory (Baselski and Wunderink, 1994; Su et al., 2020) and substantial lung (Navani et al., 2011) diseases, and can also help improve the treatment effect (Pedro et al., 2019). However, currently there is no unified conclusion on whether bronchoscopy can improve the prognoses of patients with VAP. This study used the large public Medical Information Mart for Intensive Care (MIMIC)-IV database as a basis to determine the impact of bronchoscopy on the prognoses of patients with VAP in the ICU.

METHODS

Data Source and Population

The MIMIC-IV is a large, free, and open database; the latest version is MIMIC-IV (version 1.0) (Johnson et al., 2021), which contains comprehensive information on approximately 250,000 patients hospitalized from 2008 to 2019, and provides strong data support for clinical studies (Yang et al., 2020; Wu et al., 2021). The database was approved by the Massachusetts Institute of Technology (Cambridge, Mass.) and the Beth Israel Deaconess Medical Center (Boston, Mass.), and consent was obtained for collection of the original data (Zhang et al., 2021). The database also anonymizes patient information, and so informed consent did not need to be obtained. The researchers needed to complete corresponding courses and obtain certificates to access and extract data from this database.



TABLE 1 | Baseline characteristics of original population.

No Branchessery Group Branchessery Group P-Value (Coup Branchessery Group		Orig	inal Population	PSM Population			
N 1.255 0.05 105 106 5.00 6.0		No Bronchoscopy Group	Bronchoscopy Group	<i>p</i> -Value	No Bronchoscopy Group	Bronchoscopy Group	<i>p</i> -Value
App (war) 64.00 B5.00 R2.00 B5.00 B5.00 R0.464 0.445 Mais 65.00 R2.7 135 65.00 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 65.11 127 127 127 65.21 11.11 128 <td>N</td> <td>1,355</td> <td>205</td> <td></td> <td>195</td> <td>195</td> <td></td>	N	1,355	205		195	195	
Gandar (%) (b) (b) (c) (c)<	Age (year)	64.00 (53.00, 75.00)	62.00 (50.00, 74.00)	0.302	66.00 (53.50, 76.00)	63.00 (50.00, 75.50)	0.546
Mele Fernane BEO (BZ,7) 135 (BC.6) 129 (BC.2) 127 (B7.1) Ethnicay (%) 0 0 0 0 0 0.19 Bunk 154 (11.4) 17 (BZ.7) 156 (63.8) 12 (25 (1.7) 0 0.202 (1.7) 0.012 (1.2) 0.012	Gender (%)			0.432			0.915
Fernalm 505 (F7.2) 770 (F7.4) 130 (F5.4) 155 (F3.8) 723 (F7.4) White 777 (F7.4) 130 (F5.4) 171 (F2.7) 17 (F2.7) 17 (F2.7) Others 428 (F1.7) 68 (F2.8) 73 (F7.4) 128 (F2.5) 73 (F7.4) 78 (F2.4) 78 (F2.4) PECI are unit (%) 0100 (F2.43 (F3.1) 28 (F2.5) 120 (F2.43 (F3.1) 73 (F7.4) 78 (F2.4)	Male	850 (62.7)	135 (65.9)		129 (66.2)	127 (65.1)	
Ehmachy (b), Unital T72 (67.0) T30 (63.4) T56 (53.8) T22 (67.1) Electronic (70.1) Black T41 (11.4) T7 (87.3) T7 (87.7) T5 (75.3) T2 (75.7) S5 (23.2) BM 28.25 (24.25, 53.66) 28.44 (25.63, 34.66) 0.184 29.01 (24.33, 35.15) 28.44 (25.55, 34.61) 0.484 Partine BM (20.10) D07 (75.3) T7 (87.7) T7 (87.7) T7 (87.6) T1 (16.1) S (16.2) T0.0 (57.0) 144 (24.1) 0.104 23.00 MCLUSICU TD7 (75.3) 190 (75.7) 11 (16.1) S (17.0) 11 (16.1) S (17.0) 11 (16.1) S (17.0) 11 (16.1) 13 (17.0)	Female	505 (37.3)	70 (34.1)		66 (33.8)	68 (34.9)	
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Others 4/29 (31.7) 56 (28.3) 73 (57.4) 55 (28.2) PRI 265 (24.25, 33.64) 0.286 71.00 (57.00, 94.50) 0.246 APSII 69.00 (51.00, 93.00) 70.00 (65.00, 91.00) 0.286 71.00 (57.00, 94.50) 71.00 (56.00, 91.00) 0.248 MCUSICU 1.007 (74.3) 174 (84.9) 157 (80.5) 144.600 (55.62, 287.00) 0.302 Others 344 (25.7) 31 (15.1) 38 (19.5) 31 (15.9) 1000 Controbidities 52.2.0 15 (28.5) 10.00 (65.62, 287.00) 0.302 127.00 (84.50, 243.50) 145.00 (65.62, 287.00) 0.302 Controbidities Septek (%) 1.300 (65.6) 20.00 (97.6) 0.578 192 (98.5) 190 (97.4) 0.210 Controbidities Septek (%) 1.300 (65.6) 20.00 (97.6) 0.578 192 (98.5) 19 (97.4) 0.24 (12.3) 0.200 Controbidities Septek (%) 1.000 (65.6) 27.00 (17.7) 0.40 (23.6) 0.26 (23.6) 0.476 Controbidities Septek (%) 1.011 (14.3) 0.44 (4.31.64.7	Black	154 (11.4)	17 (8.3)		17 (8.7)	17 (8.7)	
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APSIII 69.00 61.00 70.00 (50.00 71.00 (57.00 91.00 6.0426 MICU/SICU 1.007 (74.3) 174 (84.9) 157 (80.5) 114 (84.1) Others 348 (25.7) 31 (15.1) 338 (19.5) 115.00 65.00, 28.5.00 0.332 Others 148 (25.7) 31 (15.1) 36 (19.5) 5 (2.6) 5 (2.	BMI	28.25 (24.25, 33.69)	28.44 (25.60, 34.66)	0.184	29.01 (24.39, 35.15)	28.40 (25.55, 34.61)	0.844
First care unit (%) UD07 (74.3) T47 (84.9) T57 (80.5) T44 (84.1) Otherse 348 (82.57) 31 (15.1) 38 (19.5.) 31 (15.3) Duration of MV (hour) 1350 00 60.50, 253.50 145.00 (800.00, 286.00) 0.322 127.00 (84.50, 244.50) 145.00 (800.00, 286.00) 0.322 127.00 (84.50, 244.50) 145.00 (800.00, 286.00) 0.322 127.00 (84.50, 244.50) 145.00 (84.50, 244.50) 145.00 (84.50, 244.50) 10.00 (87.4) <td< td=""><td>APSIII</td><td>69.00 (51.00, 90.00)</td><td>70.00 (56.00, 91.00)</td><td>0.286</td><td>71.00 (57.00, 94.50)</td><td>71.00 (56.00, 91.00)</td><td>0.395</td></td<>	APSIII	69.00 (51.00, 90.00)	70.00 (56.00, 91.00)	0.286	71.00 (57.00, 94.50)	71.00 (56.00, 91.00)	0.395
MICUSICU 1.0.07 (rV.3) 174 (84.9) 157 (80.5) 164 (84.1) Others 948 (25.7) 31 (15.1) 38 (19.5) 31 (15.9) 0.000 Ourspressore (%) 518 (83.2) 63 (00.7) 0.46 61 (31.3) 60 (02.8) 1.000 Chront (%) 43 (3.2) 5 (2.4) 0.726 5 (2.6) 5 (2.6) 1.000 Cornorbidies Sepses (%) 1.208 (96.5) 2.200 (97.6) 0.578 192 (98.3) 190 (97.4) 0.274 Mycocredia Inferct (%) 423 (33.4) 59 (28.8) 0.214 63 (22.3) 55 (28.2) 0.400 Chronic pulmonary 338 (28.6) 70 (94.1) 0.125 62 (31.8) 66 (33.8) 0.474 Chronic pulmonary 338 (28.6) 70 (94.1) 0.125 62 (31.8) 63 (38.8) 0.768 Faread disease (%) 328 (28.6) 71 (8.0) 0.157 38 (19.5) 31 (16.9) 0.366 Liker disease (%) 328 (28.6) 70 (84.6) 0.472 33 (16.9) 0.466 0.477 (75.6) 0.466 (38.8) </td <td>First care unit (%)</td> <td></td> <td></td> <td>0.001</td> <td></td> <td></td> <td>0.426</td>	First care unit (%)			0.001			0.426
Others 348 (35.7) 31 (16.1) 38 (19.5) 31 (16.3) Duration of MV (1904) 150.00 (65.0, 227.0) 145.00 (69.0, 226.0) 0.232 127.00 (45.0, 224.5) 145.00 (65.0, 227.0) 0.206 ORRT (%) 518 (63.2) 5 (2.4) 0.726 5 (2.6) 10.00 (74.4) 0.721 0.5 (2.6) 10.00 (74.0) 0.721 0.5 (2.6) 10.00 (74.4) 0.721 0.723 0.5 (2.6) 10.00 (74.0) 0.721 0.723 0.5 (2.6) 1.702 0.721 0.723 0.721 0.723 0.723 0.724 0.723 0.724 0.721 0.746 (2.5) 0.712 0.741 0.741 0.711 0.746 (2.5) 0.747 0.741 0.742 0.723 0.744 0.742 0.741 0.741 0.711<	MICU/SICU	1,007 (74.3)	174 (84.9)		157 (80.5)	164 (84.1)	
Duration of MV (hour) 138.00 (80.05, 253.01) 145.00 (84.05, 243.0) 142.00 (84.65, 243.0) 140.00 (85.0, 257.00) 0.306 Vasopressors (%) 518 (32, 2) 65 (2.4) 0.768 52.6.0) 512.6.0 10.000 Compobilities Secsis (%) 1.308 (96.6) 200 (97.6) 0.78 142 (95.5) 190 (97.4) 0.721 Myocardial Infert (%) 257 (19.0) 24 (11.7) 0.15 34 (17.4) 24 (17.7) 0.470 0.761 Competitiones 257 (19.0) 24 (11.7) 0.144 63 (27.7) 46 (23.8) 0.746 Competitiones 346 (25.5) 47 (22.9) 0.474 54 (27.7) 46 (23.8) 0.746 Chancia Age(%) 346 (27.7) 33 (16.1) 0.412 54 (27.7) 46 (23.8) 0.746 Mail Instance (%) 308 (22.7) 33 (16.1) 0.401 41 (27.1) 33 (16.3) 0.420 Viral signs 308 (23.6) 7.61 (70.8 (23.6) 0.22 (26.7) 45 (23.1) 0.430 Viral signs 306 (19.0.17) 46 (23.4) 0.22 (Others	348 (25.7)	31 (15.1)		38 (19.5)	31 (15.9)	
Visacopressors (6) 518 (38.2) 63 (0.7) 0.046 61 (1.3) 80 (02.8) 1.000 Cornorbidities 52.6) 0.417 52.6) 0.417 52.6) 0.417 52.6) 0.417 52.6) 0.417 62.63.8) 0.416 0.411 1.101 0.30 66.33.8) 0.716 62.63.8) 0.416 0.328 0.416 0.416 0.411 0.411 1.412.610 0.321 0.425 0.425 0.426 0.426 0.426 0.426 0.426 0.426 0.426 0.426 0.426 0.426 0.426 0.426 0.426	Duration of IMV (hour)	136.00 (60.50, 253.50)	145.00 (59.00, 286.00)	0.332	127.00 (64.50, 243.50)	145.00 (56.50, 287.00)	0.306
CRHT (%) 43 (3.2) 5 (2.4) 0.726 5 (2.6) 5 (2.6) 1.000 Serpsie (%) 1.308 (96.5) 200 (97.6) 0.578 192 (96.5) 190 (97.4) 0.721 Mycoardial Infert (%) 257 (19.0) 24 (11.7) 0.015 34 (17.4) 24 (12.2) 0.200 Compassive Insert failure (%) 453 (25.5) 47 (22.5) 0.444 63 (22.5) 5 (2.6) 0.476 Cherobroacouter disease (%) 346 (25.5) 47 (22.5) 0.474 54 (27.7) 46 (23.6) 0.476 Cleases (%) 255 (18.8) 33 (16.1) 0.401 41 (21.0) 33 (16.9) 0.306 Diabetes (%) 430 (31.7) 44 (23.4) 0.02 52 (26.7) 45 (23.1) 0.402 Maigrency (%) 127 (9.4) 23 (11.2) 0.478 22 (10.6) 22 (11.3) 1.000 Wean hear tabe (mn-1) 76.4 (70.94, 85.10) 75.16 (71.04, 84.00) 0.545 75.86 (98.16, 98.29) 76.16 (70.98, 83.57) 0.309 Mean heage tabe (%) 33 (95.10) 75.16 (71.04, 84.00) 0.54	Vasopressors (%)	518 (38.2)	63 (30.7)	0.046	61 (31.3)	60 (30.8)	1.000
Cornelations of the series of	CRRT (%)	43 (3.2)	5 (2.4)	0.726	5 (2.6)	5 (2.6)	1.000
Bessie (%) 1,308 (96.5) 200 (97.4) 0.578 192 (97.4) 0.721 Mycoardial infarct (%) 257 (19.0) 24 (11.7) 0.015 34 (17.4) 24 (12.3) 0.200 Congestive heart faller (%) 453 (33.4) 69 (28.8) 0.214 63 (23.2) 55 (28.2) 0.401 Deretrovascular disease (%) 368 (25.5) 47 (22.9) 0.474 54 (27.7) 46 (23.6) 0.716 Deretrovascular disease (%) 368 (23.5) 77 (26.1) 0.125 66 (33.8) 0.746 Heral disease (%) 308 (22.7) 37 (18.0) 0.157 38 (19.5) 36 (16.5) 0.289 Maignancy (%) 127 (9.4) 23 (11.2) 0.477 21 (10.8) 22 (11.3) 1.000 Vial sign 8 77.64 (70.94, 85.10) 75.16 (70.94, 85.10) 75.16 (70.94, 85.7) 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.573 0.583 <td>Comorbidities</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Comorbidities						
Mycoardia Infarct (%) 257 (19.0) 24 (11.7) 0.015 34 (17.4) 24 (12.3) 0.20 Corgensive heart falure (%) 453 (32.4) 55 (28.5) 0.214 63 (32.3) 55 (28.2) 0.440 Cherebrossci (%) 366 (25.5) 47 (72.9) 0.474 454 (27.7) 46 (23.6) 0.417 Cherabrossci (%) 255 (18.8) 33 (16.1) 0.401 41 (21.0) 33 (16.9) 0.366 Liver disease (%) 255 (18.8) 33 (16.1) 0.401 41 (21.0) 33 (16.9) 0.366 Renal disease (%) 255 (18.8) 33 (16.1) 0.401 41 (21.0) 33 (16.9) 0.366 Wall signs 366 (18.5) 77.6 (7.044, 84 (23.4) 0.02 52 (26.7) 45 (23.1) 0.442 Wall signs 77.7 77.6 (7.044, 86.10 76.16 (7.104, 84.00 0.545 75.88 (68.11, 22.90 87.37 (75.65, 98.66) 0.309 Wall signs 77.7 77.6 (7.044, 86.10 76.16 (7.044, 84.00 0.66 0.12 (17.4, 32.03) 17.3 (17.40, 22.83) 0.400 Wale hoppretuper (%) 107.7 (66.67, 37	Sepsis (%)	1,308 (96.5)	200 (97.6)	0.578	192 (98.5)	190 (97.4)	0.721
Concessive heart faller (%) 453 (33.4) 50 (28.8) 0.214 83 (23.3) 55 (28.2) 0.440 Hypertension (%) 364 (25.5) 47 (22.9) 0.474 54 (27.7) 46 (23.6) 0.476 Crentoroascular disease (%) 388 (28.6) 70 (34.1) 0.125 52 (27.1) 66 (33.8) 0.766 Fendi disease (%) 255 (18.8) 33 (16.1) 0.401 41 (21.0) 33 (16.9) 0.368 Malgnancy (%) 127 (9.4) 23 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Waal spars (%) 127 (9.4) 23 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Waan heap remarking (%) 127 (9.4) 23 (11.2) 0.478 21 (10.8) 27 (15.6) 9.66 0.202 Mean heap remarking (%) 127 (9.4, 85.10) 78.16 (71.48, 80.0) 0.56 77.65.5 9.66 0.202 Mean segaratory rate (min-1) 85.61 (74.81; 99.31) 87.00 (75.58, 98.89) 0.701 (56.67, 37.4) 37.00 (56.6, 37.45) 0.648 20.707 (56.67, 98.74) 37.00 (56.6, 37.45) 0.649 <td< td=""><td>Myocardial infarct (%)</td><td>257 (19.0)</td><td>24 (11.7)</td><td>0.015</td><td>34 (17.4)</td><td>24 (12.3)</td><td>0.200</td></td<>	Myocardial infarct (%)	257 (19.0)	24 (11.7)	0.015	34 (17.4)	24 (12.3)	0.200
Hypertension (%) 625 (46.1) 101 (49.3) 0.444 93 (47.7) 97 (49.7) 0.76 Cerebrovascular disease (%) 346 (25.5) 47 (22.9) 0.474 54 (27.7) 46 (33.6) 0.746 Glesses (%) 368 (28.6) 70 (34.1) 0.125 62 (31.8) 66 (33.8) 0.746 Glesses (%) 368 (22.7) 37 (18.0) 0.157 38 (19.5) 36 (18.5) 0.897 Diabeties (%) 430 (31.7) 48 (23.4) 0.02 52 (26.7) 45 (23.1) 0.462 Wall agrins Y(%) 127 (9.4) 23 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Waran Mog (mm-lg) 77.64 (70.94, 85.10) 76.16 (71.04, 48.00) 0.545 75.88 (09.81, 82.97, 28) 76.16 (70.98, 83.57, 70.030) 0.309 Mean Mog (mm-lg) 77.26 (70.94, 85.10) 76.16 (71.04, 48.00) 0.545 20.12 (7.44, 23.03) 19.73 (17.40, 22.83) 0.430 Mean Mog (mm-lg) 77.26 (70.94, 87.57) 19.73 (17.40, 22.83) 0.430 1.425.00 (81.5.97, 47.23) 0.430 Mean Mog (mm-lg)	Congestive heart failure (%)	453 (33.4)	59 (28.8)	0.214	63 (32.3)	55 (28.2)	0.440
Cerebrovascular disease (%) 346 (25.5) 47 (2.9) 0.474 564 (27.7) 46 (23.6) 0.476 Chronic pulmonary 388 (28.6) 70 (24.1) 0.125 62 (31.8) 66 (33.8) 0.746 disease (%) 308 (22.7) 37 (18.0) 0.157 38 (19.5) 36 (18.5) 0.897 Diabetes (%) 430 (31.7) 44 (23.4) 0.02 52 (26.7) 45 (23.1) 0.428 Maignary (%) 127 (e.4) 23 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Waan hear trate (min-1) 86.54 (74.81, 99.31) 87.09 (75.58, 98.89) 0.701 84.37 (73.52, 97.26) 87.37 (75.65, 99.66) 0.202 Mean respiratory rate (min-1) 19.71 (73.92, 22.67) 19.73 (17.42, 22.81) 9.730 (66.51, 98.7) 9.764 (86.04, 98.7) 0.303 Mean spp22 (%) 97.38 (95.90, 98.81) 0.069 97.86 (96.15, 98.7) 97.64 (86.04, 98.7) 0.337 Unrolear 1.490.00 (185.00, 17.200 (19.50, 0. 1.412.500 (19.53, 0. 1.210 (9.40, 18.50) 1.220 (9.40, 18.50) 1.230 (9.50, 16.30) 0.438 Unrolear </td <td>Hypertension (%)</td> <td>625 (46.1)</td> <td>101 (49.3)</td> <td>0.444</td> <td>93 (47.7)</td> <td>97 (49.7)</td> <td>0.761</td>	Hypertension (%)	625 (46.1)	101 (49.3)	0.444	93 (47.7)	97 (49.7)	0.761
Chronic pulmonary 388 (28.6) 70 (34.1) 0.125 62 (31.8) 66 (33.8) 0.746 Gleeaee (%) 308 (22.7) 37 (18.0) 0.157 38 (19.5) 36 (18.5) 0.897 Dabelets (%) 308 (22.7) 37 (18.0) 0.157 38 (19.5) 36 (18.5) 0.482 Malignaroy (%) 127 (9.4) 22 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Mean heart rate (min-1) 86.54 (74.81, 99.31) 67.09 (75.85, 99.89) 0.701 84.37 (73.52, 97.26) 87.37 (75.65, 99.66) 0.309 Mean heart rate (min-1) 19.71 (17.39, 22.67) 19.73 (17.44, 22.76) 0.646 20.12 (17.44, 23.03) 19.73 (17.40, 22.83) 0.309 Mean respiratory rate (min-1) 1.77 (64 (70.94, 83.57) 0.107 37.07 (08.69, 37.42) 37.00 (08.60, 37.37) 0.309 Mean Space (%) 97.39 (65.19, 99.11) 97.38 (65.19, 98.10) 0.97 (97.66, 99.66) 0.329 Uhricoclipat 1.490.00 (859.00, 1.620.00 (90.00, 0.30) 0.311 1.425.00 (18.00, 73.71) 0.391 Uhricoclipat 215 (11.8) 3	Cerebrovascular disease (%)	346 (25.5)	47 (22.9)	0.474	54 (27.7)	46 (23.6)	0.417
Liker (%) 255 (16.8) 33 (16.1) 0.401 41 (21.0) 33 (16.5) 0.366 Penal disease (%) 308 (22.7) 37 (18.0) 0.157 38 (19.5) 36 (18.5) 0.897 Diabetes (%) 430 (31.7) 48 (23.4) 0.02 52 (26.7) 44 (23.1) 0.482 Mail agins Mail agins 77.56, 79.68, 98.80) 0.701 84.775.52, 97.26) 87.37 (75.65, 98.66) 0.202 Mean Map (mmH) 77.64 (70.49, 85.10) 76.16 (71.04, 84.00 0.545 75.88 (68.18, 28.9) 76.16 (70.98, 85.37) 0.302 Mean Map (mmH) 19.71 (17.39, 22.67) 19.73 (17.34, 22.76) 0.646 20.12 (17.44, 23.03) 19.73 (17.40, 22.83) 0.450 Mean SpOC (%) 37.07 (36.69, 37.45) 36.65 (36.60, 37.37) 0.107 27.00 (36.67, 37.42) 37.00 (36.60, 37.37) 0.328 Unrobiology (%) 11.80.00 (65.00, 1.820.00 (915.00, 8.11 1.242.00 (915.90, 1.262.00 (92.5,0) 1.37 Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) 1.230 (55.0, 15.30) 0.486	Chronic pulmonary disease (%)	388 (28.6)	70 (34.1)	0.125	62 (31.8)	66 (33.8)	0.746
Bena disease (%) 308 (22.7) 37 (18.0) 0.157 38 (19.5) 36 (18.5) 0.897 Diabetes (%) 430 (31.7) 48 (23.4) 0.02 52 (26.7) 45 (23.1) 0.487 Maignarroy (%) 127 (9.4) 23 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Waan hear rate (min-1) 86.54 (7.48.1, 99.31) 87.09 (75.58, 98.89) 0.701 84.37 (73.52, 97.26) 87.37 (75.65, 99.66) 0.202 Mean temperature (C) 37.07 (36.69, 37.45) 36.55 (36.60, 37.37) 0.107 37.07 (36.67, 37.42) 37.00 (36.60, 37.37) 0.392 Mean temperature (C) 37.07 (36.69, 37.45) 36.55 (36.60, 37.37) 0.107 37.07 (36.67, 37.42) 37.00 (36.60, 37.37) 0.392 Mean temperature (C) 37.39 (96.19, 99.11) 97.83 (95.96, 98.81) 0.069 97.86 (96.19.96, 11.40) 1.420.00 (819.50, 1.420.00 (819.50, 1.420.00 (819.50, 1.420.00 (819.50, 1.420.00 (819.50, 1.420.00 (84.7) 1.420.00 (819.50, 1.420.00 (84.7) 1.420.00 (819.50, 1.420.00 (84.7) 1.420.00 (81.50, 1.420.00 (84.7) 1.420.00 (81.50, 1.420.00 (84.7) 1.420.00 (81.50, 1.420.00 (84.7) 1.420.00 (84.7) 1.420.00 (84.7) 1.420.00 (84.7)	Liver disease (%)	255 (18.8)	33 (16.1)	0.401	41 (21.0)	33 (16.9)	0.366
Diabetes (%) 430 (31.7) 48 (23.4) 0.02 52 (26.7) 45 (23.1) 0.482 Maignanov (%) 127 (8.4) 23 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Mean haar trate (min-1) 86.54 (74.81, 99.31) 87.09 (75.58, 98.89) 0.701 84.37 (73.52, 97.26) 87.37 (75.65, 99.66) 0.202 Mean haar trate (min-1) 19.71 (17.39, 22.67) 19.73 (17.34, 22.76) 0.646 20.12 (17.44, 23.03) 19.73 (17.40, 22.83) 0.450 Mean respiratory rate (min-1) 19.71 (17.39, 22.67) 19.73 (17.34, 22.76) 0.646 20.12 (17.44, 23.03) 19.73 (17.40, 98.78) 0.338 Unneoutput (m) 1.490.00 (859.00, 1.820.00 (915.00, 0.811 1.425.00 (819.50, 1.820.00 (92.50, 0.317 Unreoutput (m) 1.490.00 (859.00, 1.820.00 (915.00, 0.811 1.425.00 (819.50, 1.820.80 0.058 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) Gram positive 211.8) 77 (19.0) Gram positive 150 (17.00, 86.50) 84.00 (76.70, 88.50) 20 (11.8) 77 (1	Renal disease (%)	308 (22.7)	37 (18.0)	0.157	38 (19.5)	36 (18.5)	0.897
Mail grancy (%) 127 (9.4) 23 (11.2) 0.478 21 (10.8) 22 (11.3) 1.000 Vilal signs	Diabetes (%)	430 (31.7)	48 (23.4)	0.02	52 (26.7)	45 (23.1)	0.482
Vital signs	Malignancy (%)	127 (9.4)	23 (11.2)	0.478	21 (10.8)	22 (11.3)	1.000
Mean heart rate (min-1) 86.54 (74.81, 99.31) 87.09 (75.58, 98.89) 0.701 84.37 (73.52, 97.26) 87.37 (75.65, 99.66) 0.202 Mean mkpp (mmHg) 77.84 (70.94, 85.10) 76.16 (71.04, 44.20) 0.546 20.12 (7.44, 23.03) 19.73 (17.30, 22.67) 0.309 Mean respiratory rate (min-1) 19.71 (17.39, 22.67) 19.73 (17.34, 22.76) 0.646 20.12 (7.44, 23.03) 19.73 (17.40, 22.88) 0.430 Mean SpC2 (%) 97.93 (96.19, 99.11) 97.63 (85.09, 68.81) 0.069 97.86 (96.15, 98.97) 97.64 (96.04, 98.78) 0.438 Unneoutput (m) 1.492.00 (95.00) 1.822.00 (915.00) 2132.50) 2292.50) 0.058 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) 364 (67.1) Gram negative 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) 12.20 (94.0, 16.10) 0.464 Nettrophils (%) 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) 229 (14.9) 17 (8.7) Laboratory tests WBC (4/Lu) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.461 (0.20, 16.00) 8.20 (76.6, 8.810)	Vital signs	(-)			()	(-)	
Mean Mbp (mmHg) 77.64 (70.94, 85.10) 76.16 (71.04, 84.00) 0.545 75.88 (69.81, 82.98) 76.16 (70.98, 83.57) 0.309 Mean respiratory rate (min-1) 19.71 (17.39, 22.67) 19.73 (17.34, 22.76) 0.107 37.07 (36.67, 37.4) 37.07 (36.68, 37.4) 37.00 (36.68, 37.4) 0.450 Mean temperature (C) 97.83 (85.99, 91.1) 97.83 (85.96, 88.81) 0.069 97.86 (96.15, 98.97) 97.64 (96.04, 98.78) 0.438 Urineoutput (ml) 1,490.00 (859.00, 1,620.00 (915.00, 0.811 1,425.00 (819.50, 1,620.00 (902.50, 0.317 Ducker 21315.00) 2285.00) 2132.50) 2292.50 0.058 Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) 37 (19.0) Cartary tests 95 (46.1) 11.80 (8.40, 16.40) 12.30 (9.50, 16.30) 0.498 WBC (k/uL) 11.80 (8.60, 16.40, 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) -0.001 83.00 (76.05, 88.10) 84.00 (76.15, 88.25) 0.625 <td>Mean heart rate (min-1)</td> <td>86.54 (74.81, 99.31)</td> <td>87.09 (75.58, 98.89)</td> <td>0.701</td> <td>84.37 (73.52, 97.26)</td> <td>87.37 (75.65, 99.66)</td> <td>0.202</td>	Mean heart rate (min-1)	86.54 (74.81, 99.31)	87.09 (75.58, 98.89)	0.701	84.37 (73.52, 97.26)	87.37 (75.65, 99.66)	0.202
Mean respiratory rate (min-1) 19.71 (17.39, 22.67) 19.73 (17.34, 22.76) 0.646 20.12 (17.44, 23.03) 19.73 (17.40, 22.83) 0.450 Mean sportature (°C) 37.07 (36.69, 37.45) 36.95 (36.60, 37.37) 0.107 37.07 (36.67, 37.42) 37.00 (36.60, 37.37) 0.392 Mean SpO2 (%) 97.33 (66.91, 99.41) 19.763 (17.64), 62.95, 98.81) 0.069 97.66 (96.15, 99.77) 74.66 (60.4), 98.75) 0.317 Microbiology (%) 2315.00) 2285.00) 2122.50) 2292.50) 0.55 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) 0.58 Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) 37.01 (8.7) Laboratory tests WEC (k/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) -0.001 83.00 (76.50, 88.10) 84.00 (76.15, 88.25) 0.625 Laboratory tests WEC (k/uL) 11.80 (8.60, 16.40, 13.00) 0.464 (1.1.00) 0.411 (9.00, 0.50) 87.00	Mean Mbp (mmHq)	77.64 (70.94, 85.10)	76.16 (71.04, 84.00)	0.545	75.88 (69.81, 82.98)	76.16 (70.98, 83.57)	0.309
Mean temperature (C) 37.07 (36.69, 37.45) 36.95 (36.60, 37.37) 0.107 37.07 (36.67, 37.42) 37.00 (36.60, 37.37) 0.392 Mean SpO2 (%) 97.93 (96.19, 99.11) 97.63 (95.99, 88.81) 0.069 97.86 (96.15, 98.97) 97.64 (96.04, 98.78) 0.438 Urineoutput (ml) 1.490.00 (659.00, 1.620.00 (915.00, 0.811 1.425.00 (819.50, 1.220.00 (92.50, 0.317 Microbiology (%) 0.2285.00) 2132.50) 2292.50) 0.058 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) Gram negative 531 (39.2) 96 (46.8) 88 (45.1) 95 (48.7) Others 160 (11.8) 17 (8.3) 29 (14.9) 17.30 (8.40, 76.15, 88.25) 0.498 Neutrophils (%) 81.00 (74.00, 66.50) 84.00 (76.70, 88.50) -0.001 8.00 (76.15, 88.25) 0.498 Umphocytes (%) 9.20 (5.70, 14.70) 8.60 (5.40, 13.00) 0.171 9.80 (5.60, 15.00) 8.70 (5.40, 13.10) 0.310 Basophils (%) 0.20 (0.00, 0.480 0.20 (0.00, 0.410 0.21 (1.00, 0.30, 0.557 0.20 (0.00, 0.400	Mean respiratory rate (min-1)	19.71 (17.39, 22.67)	19.73 (17.34, 22.76)	0.646	20.12 (17.44, 23.03)	19.73 (17.40, 22.83)	0.450
Mean Sp02 (%) 97.93 (96.19, 99.11) 97.63 (95.96, 98.81) 0.069 97.86 (96.15, 98.97) 97.64 (96.04, 98.78) 0.438 Urineoutput (mi) 1,490.00 (859.00, 1,620.00 (915.00, 0.811 1,425.00 (819.50, 1,2292.50) 0.0317 Microbiology (%) 0.120 0.120 0.120 0.058 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) 0.058 Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) 55 (28.7) 0.637 Unclear 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001	Mean temperature (°C)	37.07 (36.69, 37.45)	36.95 (36.60, 37.37)	0.107	37.07 (36.67, 37.42)	37.00 (36.60, 37.37)	0.392
Urineoutput (mi) 1,490.00 (859.00, 2315.00) 1,620.00 (915.00, 2885.00) 0.811 1,425.00 (919.50, 2132.50) 1,620.00 (902.50, 2282.50) 0.317 Microbiology (%) 0.120 0.058 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) 0.058 Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) 1.620.00 (902.50, 0.498 Others 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) 1.600 (76.0, 58.50) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001	Mean SpO2 (%)	97.93 (96.19, 99.11)	97.63 (95.96, 98.81)	0.069	97.86 (96.15, 98.97)	97.64 (96.04, 98.78)	0.438
2315.00 2285.00 2132.50 2292.50 Microbiology (%) 0.120 0.058 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) Gram negative 531 (39.2) 96 (46.8) 88 (45.1) 95 (48.7) Others 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) Laboratory tests WBC (k/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 91.00 (74.00, 86.50) 84.00 (76.70, 88.50) 0.401 9.80 (56.0, 15.00) 87.0 (54.0, 13.10) 0.310 Basophilis (%) 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.557 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.356 Eosinophilis (%) 0.60 (0.00, 1.80) 0.60 (0.10, 1.40) 0.811 0.40 (0.30, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.60, 14.60)<	Urineoutput (ml)	1,490.00 (859.00,	1,620.00 (915.00,	0.811	1,425.00 (819.50,	1,620.00 (902.50,	0.317
Microbiology (%) 0.120 0.120 0.058 Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) Gram negative 531 (33.2) 96 (46.8) 88 (45.1) 95 (48.7) Others 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) Laboratory tests WEC (k/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophile (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001		2315.00)	2285.00)		2132.50)	2292.50)	
Unclear 413 (30.5) 53 (25.9) 55 (28.2) 46 (23.6) Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) Gram negative 531 (39.2) 96 (46.8) 88 (45.1) 95 (48.7) Others 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) Laboratory tests WBC (k/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001	Microbiology (%)	,	,	0.120)	,	0.058
Gram positive 251 (18.5) 39 (19.0) 23 (11.8) 37 (19.0) Gram negative 531 (39.2) 96 (46.8) 88 (45.1) 95 (48.7) Others 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) Laboratory tests WBC (k/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001	Unclear	413 (30.5)	53 (25.9)		55 (28.2)	46 (23.6)	
Gram negative 531 (39.2) 96 (46.8) 88 (45.1) 95 (48.7) Others 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) Laboratory tests WBC (K/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001	Gram positive	251 (18.5)	39 (19.0)		23 (11.8)	37 (19.0)	
Others 160 (11.8) 17 (8.3) 29 (14.9) 17 (8.7) Laboratory tests WBC (k/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001	Gram negative	531 (39.2)	96 (46.8)		88 (45.1)	95 (48.7)	
Laboratory tests WBC (k/uL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 88.50) 84.00 (76.70, 88.50) <0.001	Others	160 (11.8)	17 (8.3)		29 (14.9)	17 (8.7)	
WBC (k/LL) 11.80 (8.60, 16.40) 12.20 (9.40, 16.10) 0.464 11.80 (8.40, 16.90) 12.30 (9.50, 16.30) 0.498 Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001	Laboratory tests		()		- (-)		
Neutrophils (%) 81.00 (74.00, 86.50) 84.00 (76.70, 88.50) <0.001 83.00 (76.05, 88.10) 84.00 (76.15, 88.25) 0.625 Lymphocytes (%) 9.20 (5.70, 14.70) 8.60 (5.40, 13.00) 0.171 9.80 (5.60, 15.00) 8.70 (5.40, 13.10) 0.310 Basophils (%) 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.557 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.356 Eosinophils (%) 0.60 (0.00, 1.80) 0.60 (0.10, 1.40) 0.891 0.40 (0.00, 1.50) 0.68 (0.10, 1.40) 0.171 Monocytes (%) 5.50 (3.60, 8.00) 4.60 (3.00, 6.00) <0.001	WBC (k/uL)	11.80 (8.60, 16.40)	12.20 (9.40, 16.10)	0.464	11.80 (8.40, 16.90)	12.30 (9.50, 16.30)	0.498
Lymphocytes (%) 9.20 (5.70, 14.70) 8.60 (5.40, 13.00) 0.171 9.80 (5.60, 15.00) 8.70 (5.40, 13.10) 0.310 Basophils (%) 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.557 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.356 Eosinophils (%) 0.60 (0.00, 1.80) 0.60 (0.10, 1.40) 0.891 0.40 (0.00, 1.50) 0.60 (0.10, 1.40) 0.171 Monccytes (%) 5.50 (3.60, 8.00) 4.60 (3.00, 6.00) <0.001 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 0.936 Hemoglobin (g/dl) 10.60 (8.80, 12.50) 10.50 (9.40, 12.30) 0.282 11.00 (9.30, 12.65) 10.50 (9.40, 12.30) 0.522 MCH (pg) 30.20 (28.60, 31.65) 30.50 (29.10, 31.70) 0.107 30.70 (29.40, 31.80) 30.40 (29.05, 31.70) 0.322 MCH (c%) 14.60 (13.55, 16.30) 14.60 (13.60, 16.10) 0.737 14.60 (13.50, 15.90) 14.50 (13.60, 16.00) 0.839 Platelet (k/uL) 189.00 (133.50, 251.00) 204.00 (21.00, 27.00) 0.114 15.00 (12.00, 17.00) 0.442 Bicarbonate (mEq/L) 15.00 (12.00, 18.00) 14.00 (12.00, 17.00) 0.114 </td <td>Neutrophils (%)</td> <td>81.00 (74.00, 86.50)</td> <td>84.00 (76.70, 88.50)</td> <td><0.001</td> <td>83.00 (76.05, 88.10)</td> <td>84.00 (76.15, 88.25)</td> <td>0.625</td>	Neutrophils (%)	81.00 (74.00, 86.50)	84.00 (76.70, 88.50)	<0.001	83.00 (76.05, 88.10)	84.00 (76.15, 88.25)	0.625
Basophils (%) 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.557 0.20 (0.00, 0.40) 0.20 (0.00, 0.30) 0.356 Eosinophils (%) 0.60 (0.00, 1.80) 0.60 (0.10, 1.40) 0.891 0.40 (0.00, 1.50) 0.60 (0.10, 1.40) 0.171 Monocytes (%) 5.50 (3.60, 8.00) 4.60 (3.00, 6.00) <0.001 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 0.936 Hemoglobin (g/dl) 10.60 (8.80, 12.50) 10.50 (9.40, 12.30) 0.282 11.00 (9.30, 12.65) 10.50 (9.40, 12.30) 0.537 MCH (pg) 30.20 (28.60, 31.65) 30.50 (29.10, 31.70) 0.107 30.70 (29.40, 31.80) 33.20 (31.85, 34.40) 0.786 RDW (%) 14.60 (13.55, 16.30) 14.60 (13.60, 16.10) 0.737 14.60 (13.50, 15.90) 14.50 (13.60, 16.00) 0.432 Anion Gap (mEq/L) 15.00 (12.00, 18.00) 14.00 (12.00, 17.00) 0.114 15.00 (12.00, 17.00) 14.00 (12.00, 17.00) 0.400 (12.00, 17.00) 0.400 (12.00, 17.00) 0.432 Bicarbonate (mEq/L) 22.00 (19.00, 25.00) 24.400 (21.00, 27.00) <0.001 24.00 (21.00, 27.50) 24.00 (21.00, 27.00) 1.000	Lymphocytes (%)	9.20 (5.70, 14.70)	8.60 (5.40, 13.00)	0.171	9.80 (5.60, 15.00)	8.70 (5.40, 13.10)	0.310
Eosinophilis (%)0.60 (0.00, 1.80)0.60 (0.10, 1.40)0.8910.40 (0.00, 1.50)0.60 (0.10, 1.40)0.171Monocytes (%)5.50 (3.60, 8.00)4.60 (3.00, 6.00)<0.001	Basophils (%)	0.20 (0.00, 0.40)	0.20 (0.00, 0.30)	0.557	0.20 (0.00, 0.40)	0.20 (0.00, 0.30)	0.356
Monocytes (%) 5.50 (3.60, 8.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 4.60 (3.00, 6.00) 9.936 Hemoglobin (g/dl) 10.60 (8.80, 12.50) 10.50 (9.40, 12.30) 0.282 11.00 (9.30, 12.65) 10.50 (9.40, 12.30) 0.543 MCH (pg) 30.20 (28.60, 31.65) 30.50 (29.10, 31.70) 0.107 30.70 (29.40, 31.80) 30.40 (29.05, 31.70) 0.322 MCHC (%) 32.70 (31.50, 33.80) 33.20 (31.80, 34.40) <0.001	Eosinophils (%)	0.60 (0.00, 1.80)	0.60 (0.10, 1.40)	0.891	0.40 (0.00, 1.50)	0.60 (0.10, 1.40)	0.171
Hemoglobin (g/d)10.60 (8.80, 12.50)10.50 (9.40, 12.30)0.28211.00 (9.30, 12.65)10.50 (9.40, 12.30)0.543MCH (pg)30.20 (28.60, 31.65)30.50 (29.10, 31.70)0.10730.70 (29.40, 31.80)30.40 (29.05, 31.70)0.322MCHC (%)32.70 (31.50, 33.80)33.20 (31.80, 34.40)<0.001	Monocytes (%)	5.50 (3.60, 8.00)	4.60 (3.00, 6.00)	< 0.001	4.60 (3.00, 6.00)	4.60 (3.00, 6.00)	0.936
MCH (pg) 30.20 (28.60, 31.65) 30.50 (29.10, 31.70) 0.107 30.70 (29.40, 31.80) 30.40 (29.05, 31.70) 0.322 MCHC (%) 32.70 (31.50, 33.80) 33.20 (31.80, 34.40) <0.001	Hemoalobin (a/dl)	10.60 (8.80, 12.50)	10.50 (9.40, 12.30)	0.282	11.00 (9.30, 12.65)	10.50 (9.40, 12.30)	0.543
MCHC (%) 32.70 (31.50, 33.80) 33.20 (31.80, 34.40) <0.001 33.30 (32.10, 34.20) 33.20 (31.85, 34.40) 0.786 RDW (%) 14.60 (13.55, 16.30) 14.60 (13.60, 16.10) 0.737 14.60 (13.50, 15.90) 14.50 (13.60, 16.00) 0.849 Platelet (k/uL) 189.00 (133.50, 251.00) 204.00 (138.00, 277.00) 0.096 186.00 (146.50, 250.00) 204.00 (136.50, 275.50) 0.391 Anion Gap (mEq/L) 15.00 (12.00, 18.00) 14.00 (12.00, 17.00) 0.114 15.00 (12.00, 17.00) 0.432 Bicarbonate (mEq/L) 22.00 (19.00, 25.00) 24.00 (21.00, 27.00) <0.001	MCH (pa)	30.20 (28.60, 31.65)	30.50 (29.10, 31.70)	0.107	30.70 (29.40, 31.80)	30.40 (29.05, 31.70)	0.322
RDW (%) 14.60 (13.55, 16.30) 14.60 (13.60, 16.10) 0.737 14.60 (13.50, 15.90) 14.60 (13.60, 16.00) 0.849 Platelet (k/uL) 189.00 (133.55, 16.30) 14.60 (13.60, 16.10) 0.737 14.60 (13.50, 15.90) 204.00 (136.50, 275.50) 0.391 Anion Gap (mEq/L) 15.00 (12.00, 18.00) 14.00 (12.00, 17.00) 0.114 15.00 (12.00, 17.00) 14.00 (12.00, 17.00) 0.414 Bicarbonate (mEq/L) 22.00 (19.00, 25.00) 24.00 (21.00, 27.00) <0.001	MCHC (%)	32.70 (31.50, 33.80)	33.20 (31.80, 34.40)	< 0.001	33.30 (32.10, 34.20)	33.20 (31.85, 34.40)	0.786
Platelet (k/uL) 189.00 (133.50, 251.00) 204.00 (138.00, 277.00) 0.096 186.00 (146.50, 250.00) 204.00 (136.50, 275.50) 0.391 Anion Gap (mEq/L) 15.00 (12.00, 18.00) 14.00 (12.00, 17.00) 0.114 15.00 (12.00, 17.00) 14.00 (12.00, 17.00) 0.432 Bicarbonate (mEq/L) 22.00 (19.00, 25.00) 24.00 (21.00, 27.00) <0.001	BDW (%)	14 60 (13 55 16 30)	14 60 (13 60, 16 10)	0 737	14 60 (13 50, 15 90)	14 50 (13 60, 16 00)	0.849
Anion Gap (mEq/L) 15.00 (12.00, 18.00) 14.00 (12.00, 17.00) 0.114 15.00 (12.00, 17.00) 14.00 (12.00, 17.00) 0.432 Bicarbonate (mEq/L) 22.00 (19.00, 25.00) 24.00 (21.00, 27.00) <0.001	Platelet (k/uL)	189.00 (133.50, 251.00)	204.00 (138.00, 277.00)	0.096	186.00 (146.50, 250.00)	204.00 (136.50, 275.50)	0.391
Bicarbonate (mEq/L) 22.00 (19.00, 25.00) 24.00 (21.00, 27.00) 24.00 (21.00, 27.50) 24.00 (21.00, 27.50) 24.00 (21.00, 27.50) 1.000 Total calcium (mEq/L) 8.20 (7.70, 8.80) 8.30 (7.80, 8.90) 0.062 8.40 (7.80, 8.90) 8.30 (7.80, 8.90) 0.791 Free calcium (mEq/L) 1.11 (1.04, 1.16) 1.11 (1.05, 1.17) 0.099 1.11 (1.05, 1.16) 1.11 (1.05, 1.17) 0.546 Magnesium (mEq/L) 1.90 (1.70, 2.20) 2.00 (180, 2.20) 0.105 1.90 (1.80, 2.20) 2.00 (1.80, 2.20) 0.694 Phosphate (mEq/L) 3.60 (2.90, 4.50) 3.70 (3.10, 4.60) 0.121 3.50 (2.90, 4.70) 3.60 (3.05, 4.55) 0.390 Sodium (mEq/L) 139.00 (136.00, 143.00) 140.00 (136.00, 142.00) 0.763 139.00 (137.00, 143.00) 140.00 (136.00, 142.00) 0.876 Votassium (mEq/L) 139.00 (136.00, 143.00) 4.10 (3.70, 4.50) 0.712 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.876	Anion Gap (mEq/L)	15.00 (12.00, 18.00)	14 00 (12 00 17 00)	0 114	15.00 (12.00, 17.00)	14 00 (12 00 17 00)	0 432
Total calcium (mEq/L) 8.20 (7.70, 8.80) 8.30 (7.80, 8.90) 0.062 8.40 (7.80, 8.90) 8.30 (7.80, 8.90) 0.791 Free calcium (mEq/L) 1.11 (1.04, 1.16) 1.11 (1.05, 1.17) 0.099 1.11 (1.05, 1.16) 1.11 (1.05, 1.17) 0.564 Magnesium (mEq/L) 1.90 (1.70, 2.20) 2.00 (1.80, 2.20) 0.105 1.90 (1.80, 2.20) 2.00 (1.80, 2.20) 0.694 Phosphate (mEq/L) 3.60 (2.90, 4.50) 3.70 (3.10, 4.60) 0.121 3.50 (2.90, 4.70) 3.60 (3.05, 4.55) 0.390 Sodium (mEq/L) 139.00 (136.00, 143.00) 140.00 (136.00, 142.00) 0.763 139.00 (137.00, 143.00) 140.00 (136.00, 142.00) 0.876 Vetassium (mEq/L) 1.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.712 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.876	Bicarbonate (mEq/L)	22 00 (19 00, 25 00)	24 00 (21 00 27 00)	<0.001	24.00 (21.00, 27.50)	24 00 (21 00 27 00)	1 000
Free calcium (mEq/L) 1.11 (1.05, 1.16) 1.11 (1.05, 1.17) 0.099 1.11 (1.05, 1.16) 1.11 (1.05, 1.17) 0.546 Magnesium (mEq/L) 1.90 (1.70, 2.20) 2.00 (1.80, 2.20) 0.105 1.90 (1.80, 2.20) 2.00 (1.80, 2.20) 0.694 Phosphate (mEq/L) 3.60 (2.90, 4.50) 3.70 (3.10, 4.60) 0.121 3.50 (2.90, 4.70) 3.60 (3.05, 4.55) 0.390 Sodium (mEq/L) 139.00 (136.00, 143.00) 140.00 (136.00, 142.00) 0.763 139.00 (137.00, 143.00) 140.00 (136.00, 142.00) 0.876 Potassium (mEq/L) 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.712 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.876	Total calcium (mEq/L)	8 20 (7 70 8 80)	8 30 (7 80 8 90)	0.062	8 40 /7 80 8 901	8 30 (7 80 8 90)	0 701
Magnesium (mEq/L) 1.90 (1.70, 2.20) 2.00 (1.80, 2.20) 0.105 1.90 (1.80, 2.20) 2.00 (1.80, 2.20) 0.694 Phosphate (mEq/L) 3.60 (2.90, 4.50) 3.70 (3.10, 4.60) 0.121 3.50 (2.90, 4.70) 3.60 (3.05, 4.55) 0.390 Sodium (mEq/L) 139.00 (136.00, 143.00) 140.00 (136.00, 142.00) 0.763 139.00 (137.00, 143.00) 140.00 (136.00, 142.00) 0.876 Potassium (mEq/L) 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.712 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.876	Free calcium (mEq/L)	1 11 (1 04 1 16)	1 11 (1 05 1 17)	0.002			0.546
Phosphate (mEq/L) 3.60 (2.90, 4.50) 3.70 (3.10, 4.60) 0.121 3.50 (1.00, 2.20) 2.00 (1.00, 2.20) 0.1094 Sodium (mEq/L) 3.60 (2.90, 4.50) 3.70 (3.10, 4.60) 0.121 3.50 (2.90, 4.70) 3.60 (3.05, 4.55) 0.390 Sodium (mEq/L) 139.00 (136.00, 143.00) 140.00 (136.00, 142.00) 0.763 139.00 (137.00, 143.00) 140.00 (136.00, 142.00) 0.903 Potassium (mEq/L) 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.712 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.876	Magnesium (mEq/L)	190 (170 220)	2 00 (1 80 2 20)	0.105	1.90 (1.80. 2.20)	2 00 (1 80 2 20)	0.6940
Sodium (mEq/L) 139.00 (136.00, 143.00) 140.00 (136.00, 142.00) 0.763 139.00 (137.00, 143.00) 140.00 (136.00, 142.00) 0.903 Potassium (mEq/L) 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.712 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.876	Phosphate (mFa/L)	3 60 (2 90 / 50)	3 70 (3 10 / 60)	0.100	3.50 (2.00, 2.20)	3 60 (3 05 4 55)	0.004
Potassium (mEq/L) 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.712 4.10 (3.70, 4.60) 4.10 (3.70, 4.50) 0.876 (Continued on following page) (Continued on following page) (Continued on following page) (Continued on following page)	Sodium (mEq/L)	139 00 (136 00 143 00)	140.00 (136.00 143.00)	0.762	139 00 (137 00 143 00)	140 00 (136 00 143 00)	0.000
(Continued on following nage)	Potassium (mEq/L)	4 10 (3 70 4 60)	4 10 (3 70 4 50)	0.712	4 10 (3 70 4 60)	4 10 (3 70 4 50)	0.876
				J.1 12		(Continued on followi	na paae)

TABLE 1	(Continued)	Baseline	characteristics	of	original po	opulation.
	(00/10/1000)	Dascinic	01101001010100	U.	ongina po	spulation.

	Orig	inal Population	PSM Population			
	No Bronchoscopy Group	Bronchoscopy Group	<i>p</i> -Value	No Bronchoscopy Group	Bronchoscopy Group	<i>p</i> -Value
PaCO2 (mmHg)	41.00 (35.00, 50.00)	43.00 (37.00, 55.00)	0.004	43.00 (36.50, 51.50)	43.00 (37.00, 54.50)	0.981
PaO2 (mmHg)	106.00 (65.00, 192.00)	122.00 (84.00, 209.00)	0.006	127.00 (81.00, 218.00)	122.00 (84.00, 210.00)	0.956
Lactate (g/dl)	1.70 (1.10, 2.70)	1.50 (1.00, 2.70)	0.061	1.60 (1.15, 2.60)	1.50 (1.00, 2.70)	0.266
Creatinine (g/dl)	1.00 (0.80, 1.70)	1.00 (0.70, 1.60)	0.161	1.00 (0.80, 1.65)	1.00 (0.70, 1.60)	0.174
Glucose (mg/dl)	139.00 (111.00, 181.00)	131.00 (109.00, 168.00)	0.058	136.00 (111.00, 167.50)	133.00 (110.00, 168.00)	0.600
INR	1.30 (1.10, 1.50)	1.20 (1.10, 1.40)	0.217	1.30 (1.10, 1.50)	1.20 (1.10, 1.40)	0.208
PTT (s)	30.60 (26.90, 38.00)	30.80 (27.30, 37.70)	0.688	31.60 (27.20, 39.60)	30.80 (27.35, 37.60)	0.404
ALT (iu/L)	30.00 (17.00, 61.00)	34.00 (18.00, 67.00)	0.16	28.00 (17.00, 63.50)	34.00 (18.00, 69.50)	0.325
AP (iu/L)	78.00 (57.00, 114.00)	81.00 (54.00, 114.00)	0.911	76.00 (57.00, 108.50)	81.00 (54.50, 115.00)	0.692
Total bilirubin (mg/dl)	0.60 (0.40, 1.10)	0.60 (0.40, 1.10)	0.821	0.60 (0.40, 1.00)	0.60 (0.40, 1.10)	0.964
Albumin (g/dl)	2.90 (2.50, 3.30)	2.90 (2.60, 3.50)	0.309	3.00 (2.60, 3.40)	2.90 (2.60, 3.50)	0.334
Delta-WBC	-1.00 (-4.55, 2.60)	-1.20 (-5.20, 2.40)	0.488	-1.20 (-4.62, 1.83)	-1.15 (-5.40, 2.63)	0.934
Delta-RDW	0.50 (-0.10, 1.70)	0.30 (-0.30, 1.30)	0.046	0.60 (0.00, 1.50)	0.35 (-0.30, 1.40)	0.353
Delta-platelet	58.50 (-9.00, 176.25)	106.00 (-0.50, 208.50)	0.048	64.00 (-1.00, 177.00)	104.00 (-6.50, 208.75)	0.192

ICU patients diagnosed with VAP in the MIMIC-IV database were included. For patients admitted to the ICU more than once, only information on the first admission was obtained. Patients without a detailed record of ventilator use or who stayed in the ICU for less than 24 h were excluded. Patients were divided based on whether or not they had undergone bronchoscopy during IMV.

Data Extraction

Data with less than 20% missing values in the database were extracted using Structured Query Language. The included demographic information were age, sex, body mass index (BMI), and race. Other information included the first care unit, disease severity [Acute Physiology Score III (APSIII)], interventional therapy [vasopressor use, continuous renal replacement therapy (CRRT) use, and duration of IMV], major comorbidities [sepsis, myocardial infarction (MI), congestive heart failure (CHF), hypertension, cerebrovascular disease (CD), chronic pulmonary disease (CPD), liver disease (LD), renal disease (RD), diabetes, and malignancy]; microbiology; results of the first laboratory tests after ICU admission [white blood cells (WBC), neutrophils, lymphocytes, basophils, eosinophils, monocytes, red blood cells (RBC), hematocrit, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), platelets, anion gap (AG), calcium total, calcium bicarbonate. free. magnesium phosphate, chloride, sodium, potassium, base excess (BE), calculated total CO2, pH, PaCO2, PaO2, lactate, creatinine, blood urea nitrogen (BUN), glucose, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time aspartate aminotransferase (AST), (PTT), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), total bilirubin, and albumin], and vital signs within 24 h of ICU admission [mean heart rate (mHR), mean value of mean arterial pressure (mMAP), mean respiratory rate (mRR), mean temperature (mT), mean SpO2(mSpO2), urine output].

The outcomes of this study were ICU and in-hospital mortality.

Statistical Analyses

In this study, Pearson's correlation coefficient was adopted to determine the correlation between characteristic variables and to remove strongly correlated variables (Zhang et al., 2022). The following variables had coefficients higher than 0.6, so were removed since they were considered strongly correlated: RBC, hematocrit, MCV, chloride, BE, calculated total CO_2 , pH, BUN, PT, AST, and LD (**Supplementary Figure S1**). For other variables with less than 20% of missing values, the "mice" package of R software was used to perform multiple imputation.

The data for continuous variables were represented as mean and standard-deviation or median and interquartile (IQR) values, while those for categorical data were represented as frequencies. The Mann-Whitney U test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables.

The Kaplan-Meier (KM) method draws a cumulative incidence curve, indicating the occurrence of ICU and inhospital deaths in different groups of patients, and the differences in risk between the groups were compared using log-rank tests. Furthermore, after adjusting different covariates, two Cox proportional-hazards models were constructed to analyze the influence of the relationship between bronchoscopy and outcomes. There were no adjustments for covariates in model I. In model II, all variables, including age, sex, race, BMI, first care unit, APSIII, vasopressors, CRRT, duration of IMV, sepsis, MI, CHF, hypertension, CD, CPD, LD, RD, diabetes, malignancy, WBC, neutrophils, lymphocytes, basophils, eosinophils, monocytes, hemoglobin, MCH, MCHC, RDW, platelet, AG, bicarbonate, calcium total, calcium free, magnesium phosphate, sodium, potassium, PaCO2, PaO2, lactate, creatinine, glucose, INR, PTT, ALT, AP, bilirubin total, albumin, mHR, mMAP, mRR, mT, mSpO2, urine output were



adjusted for confounding factors. In the multivariate COX regression, we also evaluated the multicollinearity between the variables using variance inflation factors (VIF). **Supplementary Table S1** revealed that the VIF of each variable was less than 4, indicating that there was no multicollinearity between them.

To ensure that the results were stable and reliable, we further adjusted for covariates using propensity score matching (PSM) and propensity score-based inverse probability of treatment (IPTW) after analyzing the original population. Multivariate logistic regression model was used to estimate patient propensity scores by using one-to-one nearest neighbor matching with a caliper width of 0.05. The IPTW model was created using estimated propensity scores as weights. Differences in baseline levels between the two groups were evaluated using p values. Then, COX regression was performed on the matched population and the weighted population, respectively.

Causal mediation analysis (CMA) can distinguish the total effect of treatment into direct effects and indirect effects. If the independent variable X has a certain influence on the dependent variable Y through a certain variable M, then M is called the mediating variable of X and Y (Imai et al., 2010). In the present study, we hypothesized that changes in a particular indicator were mediating variables, that is, we assumed that bronchoscopy might lead to changes in that indicator and that such changes were



population; (B,D,F) are the in-hospital mortality risk for the original population, the PSM population and t

Outcomes	Model	I	Model II		
	HR (95%CI)	<i>p</i> -Value	HR (95%CI)	p-Value	
Original population					
ICU Mortality					
Bonchoscopy					
no	Reference		Reference		
yes	0.44 (0.29,0.68)	<0.001	0.33 (0.20,0.55)	<0.001	
In-hospital Mortality Bonchoscopy					
no	Reference		Reference		
yes	0.49 (0.33,0.72)	< 0.001	0.40 (0.26,0.60)	< 0.001	
After PSM					
ICU Mortality					
Bonchoscopy					
no	Reference		Reference		
yes	0.36 (0.21,0.61)	<0.001	0.33 (0.17,0.64)	0.001	
In-hospital Mortality					
Bonchoscopy					
no	Reference		Reference		
yes	0.38 (0.24,0.59)	<0.001	0.33 (0.20,0.58)	< 0.001	
After IPTW					
ICU Mortality					
Bonchoscopy					
no	Reference		Reference		
yes	0.37 (0.23,0.60)	<0.001	0.26 (0.14,0.50)	< 0.001	
In-hospital Mortality					
Bonchoscopy					
no	Reference		Reference		
yes	0.42 (0.27,0.65)	<0.001	0.35 (0.21,0.57)	<0.001	

TABLE 2 | Results of Cox proportional hazard models.

associated with the prognosis of VAP patients. The average causal mediating effect (ACME), average direct effect (ADE) and total effect obtained through CMA can help us verify the above

conjecture. Finally, WBC, platelets and RDW, three indicators that were further investigated for the presence of mediating effects because of their low absence rate after the cessation of IMV. Their change level was expressed as the difference between the corresponding first examination results and recorded as delta-WBC, delta-RDW, delta-platelet.

We also analyzed the impact of bronchoscopy on the prognoses of patients from different subgroups. The subgroups included age (dichotomized at 65 years), sex, type of first care unit, APSIII (dichotomized at the median of 69), and all comorbidities. The interactions between subgroups were further analyzed.

A two-tailed probability value of p < 0.05 was considered statistically significant. All statistical analyses in this study were performed using R software (version 4.1.0).

RESULTS

Baseline Characteristics

This study enrolled 1,560 patients with VAP: 1,355 in the nobronchoscopy group and 205 in the bronchoscopy group (Figure 1). The median (IQR) ages of the patients in these two groups were 64.00 years (53.00-75.00 years) and 62.00 years (50.00-74.00 years), respectively; there were more male patients in the two groups (62.7 and 65.9%, respectively); the median (IQR) APSIII were 69.00 (51.00-90.00) and 70.00 (56.00-91.00), respectively; the median (IQR) durations of IMV were 136.00 h (60.50–253.50 h) and 145.00 h (59.00-286.00 h), respectively; and sepsis was the most common complication, present in 96.5 and 97.6% of patients in the two groups, respectively. The remaining baseline characteristics of the patients are listed in detail in Table 1.



Survival Analysis and Cox Proportional-Hazards Regression Model

The KM survival curve in **Figure 2** indicated a significant difference in survival probability between the two groups. The survival probability in the ICU and in hospital was significantly higher in the bronchoscopy group than in the no-bronchoscopy group (**Figure 2**). The results of

the log-rank test indicated that the mortality risks in the ICU and in hospital differed between the two groups.

 Table 2 lists the results for the Cox proportional-hazards model.

 In two models with no adjustment for confounders, or adjustment for all confounders, the hazard ratio (HR) was significantly lower than one for the bronchoscopy group compared with the no-bronchoscopy

TABLE 3 | Subgroup analysis of relationship between groups and mortality.

	ICU Mortality			Hospital Mortality		
	HR (95%CI)	p-value	p-interaction	HR (95%CI)	p-value	p-interaction
Age			0.773			0.442
<65 (n = 791)	0.61 (0.26,1.44)	0.261		0.59 (0.28,1.25)	0.167	
≥65 (n = 769)	0.28 (0.15,0.53)	< 0.001		0.34 (0.20,0.57)	<0.001	
Gender			0.055			0.150
Male $(n = 985)$	0.23 (0.11.0.46)	<0.001		0.32 (0.18.0.55)	<0.001	
Female ($n = 575$)	0.36 (0.17.0.82)	0.014		0.47 (0.23.0.92)	0.029	
First care unit	(- , ,		0.941	(******		0.576
MICU/SICU ($n = 1.181$)	0.32 (0.18.0.56)	< 0.001		0.35 (0.22.0.57)	< 0.001	
Others $(n = 379)$	0.30 (0.09 1.03)	0.056		0.44 (0.16.1.16)	0.097	
APSIII	0100 (0100) 1100)	0.000	0.381	0111 (0110) 1110)	0.001	0.390
< 69 (n = 763)	0.49 (0.18.1.36)	0 170	0.001	0.40 (0.17.0.93)	0.032	0.000
>69 (n - 797)	0.30 (0.17.0.54)	<0.001		0.36 (0.22.0.59)	<0.002	
Microbiology	0.00 (0.11,0.01)	(0.001	0 162	0.00 (0.22,0.00)	(0.001	0 597
G_{ram} positive $(n - 200)$	0.46 (0.08.2.40)	0.360	0.102	0.36 (0.11.1.20)	0.005	0.037
Gram positive $(n = 290)$	0.40 (0.00,2.49)	0.003		0.30 (0.11,1.20)	0.095	
	0.27 (0.11,0.04)	0.005		0.55 (0.16,0.00)	0.002	
	NIA			NIA		
NO(7 = 52)		-0.001			-0.001	
Yes (7 = 1,508)	0.33 (0.20,0.55)	<0.001	0.007	0.39 (0.25,0.59)	<0.001	0.110
	0.44 (0.00.0.75)	0.000	0.007	0.44 (0.00.0.70)	0.001	0.118
No $(r) = 1,279$	0.44 (0.26,0.75)	0.002		0.44 (0.28,0.70)	<0.001	
Yes $(n = 281)$	0.21 (0.05,0.86)	0.031	0.007	0.24 (0.07,0.82)	0.022	0.017
Congestive heart failure	0.45 (0.04.0.04)	0.010	0.207		0.004	0.647
No $(n = 1,048)$	0.45 (0.24,0.84)	0.012		0.39 (0.23,0.67)	< 0.001	
Yes $(n = 512)$	0.17 (0.07,0.42)	<0.001		0.31 (0.15,0.61)	<0.001	
Hypertension			0.317			0.725
No (n = 834)	0.22 (0.10,0.48)	<0.001		0.35 (0.20,0.63)	<0.001	
Yes $(n = 726)$	0.33 (0.16,0.68)	0.003		0.28 (0.14,0.56)	<0.001	
Cerebrovascular disease			0.240			0.223
No (n = 1,167)	0.28 (0.15,0.51)	<0.001		0.40 (0.25,0.64)	<0.001	
Yes (n = 393)	0.31 (0.09,1.02)	0.054		0.34 (0.13,0.89)	0.028	
Chronic pulmonary disease			0.004			0.151
No $(n = 1, 102)$	0.55 (0.30,1.01)	0.053		0.48 (0.28,0.82)	<0.001	
Yes (n = 458)	0.13 (0.05,0.34)	<0.001		0.16 (0.07,0.36)	<0.001	
Renal disease			0.563			0.556
No (n = 1,215)	0.29 (0.16,0.54)	< 0.001		0.36 (0.21,0.59)	< 0.001	
Yes (n = 345)	0.36 (0.12,1.08)	0.069		0.50 (0.22,1.13)	0.096	
Liver disease			0.015			0.379
No (n = 1,272)	0.24 (0.13,0.45)	< 0.001		0.36 (0.22,0.57)	< 0.001	
Yes $(n = 288)$	0.64 (0.18,2.27)	0.491		0.56 (0.21,1.50)	0.246	
Diabetes			0.563			0.549
No (n = 1,082)	0.38 (0.21,0.68)	0.001		0.43 (0.27,0.69)	<0.001	
Yes $(n = 478)$	0.36 (0.11.0.94)	0.039		0.16 (0.07.0.36)	<0.001	
Malignant cancer	· · · · · /			· · · · · · · /		
No $(n = 1,410)$	0.25 (0.14.0.44)	<0.001		0.33 (0.21.0.53)	<0.001	
Yes (n = 150)	NA			NA		

group. In other words, compared with patients in the nobronchoscopy group, those in the bronchoscopy group had a lower risk of ICU and in-hospital mortality. In model II, after adjusting for all covariates as confounding factors, the HR (95% CI) values for ICU and in-hospital mortality in the bronchoscopy group were 0.33 (0.20–0.55) and 0.40 (0.26–0.60), respectively, indicating that the risks of ICU and in-hospital mortality were 0.67 and 0.60 lower than in the no-bronchoscopy group. (**Table 2**).

Propensity Score Matching and Inverse Probability of Treatment Weighing

After PSM and IPTW, there was no significant difference in baseline levels between the two groups (Supplementary Table S2). Kaplan-

Meier survival curves of matched and weighted populations are consistent with the original population (**Figure 2**). Univariate and multivariate COX regressions were then performed on the matched and weighted populations, respectively, yielding results consistent with the original population (**Table 2**). After multivariate COX regression, HR (95% CI) values for ICU mortality in the bronchoscopy group were 0.33 (0.17,0.64) and 0.26 (0.14,0.50), and in-hospital mortality the HR (95% CI) values of 0.33 (0.20,0.58) and 0.35 (0.21,0.57), respectively.

Causal Mediation Analysis

In the CMA analysis, after analyzing the three indicators, only the changes of RDW were significant. **Figures 3A, B** showed that in terms of in-hospital mortality of VAP patients, delta-RDW mediated 8% (95% CI:1–26%; p = 0.02) of the beneficial effect

of bronchoscopy (ACME:p = 0.02). At the same time, **Figures 3C**, **D** implied that in terms of ICU mortality, delta-RDW mediated 7% (95% CI: 1–21%; p = 0.02) of the beneficial effects of bronchoscopy (ACME:p = 0.02).

Subgroup Analysis

There was no significant difference between the subgroups of inhospital mortality, meaning that no interaction was present. However, bronchoscopy was associated with a reduced risk of ICU mortality in MI and CPD populations, with HRs (95% CI) of 0.21 (0.05–0.86) and 0.13 (0.05–0.34), respectively. Meanwhile, patients without LD were more likely to benefit from bronchoscopy than those with LD (HR = 0.29, 95% CI = 0.16–0.54) (**Table 3**).

DISCUSSION

Few previous studies have investigated the prognostic effects of bronchoscopy among patients with VAP, with many studying the value of bronchoscopy for diagnosing or preventing VAP (Timsit et al., 2001), or limited to specific populations such as trauma or pediatric patients (Bush, 2003; Nannapaneni et al., 2021). The present study included patients with VAP from the large public MIMIC-IV database as the study population. In this present study, we took the VAP patients in the large public database MIMIC-IV as the study population, whether it was univariate analysis, or adjusted for a number of confounding factors such as demography, intervention, disease severity score, complications, vital signs, laboratory examination indicators, etc., and reached a consistent conclusion, that is, in patients with IMV in ICU, the risk of ICU mortality and inhospital mortality in VPA patients who underwent bronchoscopy were significantly lower than those who did not receive bronchoscopy. In addition, after PSM and IPTW, the trend was consistent with that of the original population, which proved that our results were robust and reliable.

We believe that most VAP patients in the ICU are critically ill patients with severe diseases such as sepsis (Markwart et al., 2020), with unclear self-consciousness (Hübscher and Isenmann, 2016) and poor sputum expectoration ability (Tang et al., 2011), causing large amounts of sputum or respiratory secretions cannot be discharged and block the trachea, aggravating the condition. At the same time, there are a large number of inflammatory factor secretions in the patient's airway, forming a cascade amplification effect, which can spread to cause systemic inflammation (Zaragoza et al., 2020), which seriously affects the patient's prognosis. While bronchoscopy can go deep into the lower respiratory tract and directly reach the lungs with the most severe disease (Estella, 2012). When patients are undergoing IMV, bronchoscopy can not only help suck out the obstructions such as sputum and foreign bodies in the trachea, remove secretions, but also repeatedly suction and wash the lungs, which is of great significance for reducing inflammation and improving lung ventilation.

RDW is a parameter that reflects the heterogeneity of red blood cells in the blood, and is also a new marker of inflammation (Hou et al., 2018). At present, there are a lot of published evidences indicating that there is an inseparable connection between RDW and inflammatory response (Fava et al., 2019; Jandaghian et al., 2021). The inflammatory

response causes red blood cell maturation disorder through iron metabolism disorder and erythropoietin destruction, resulting in immature red blood cells into the bloodstream, but also reduce the survival rate of red blood cells, resulting in the mixing of red blood cell volume in circulation and other ways to change RDW (Salvagno et al., 2015). And some other studies have also shown that RDW is related to some conventional inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, tumor necrosis factor- α and interleukin-6 (He et al., 2018; Fava et al., 2019). In the CMA analysis, we have demonstrated that the beneficial effects of bronchoscopy on VAP patients are partially mediated by changes in RDW levels. Bronchoscopy is also essential for clinical targeted antimicrobial therapy to control inflammation, as it helps to obtain more accurate etiology, resulting in better diagnostic information. The findings of Christopher et al. showed that diagnostic bronchial therapy can help reduce the use of antibiotics and shorten the length of hospital stay (Guidry et al., 2014). Another retrospective study also indicated that the correct use of bronchoscopy can help intensive care clinicians formulate specific antibacterial treatments (Allen et al., 1994). Therefore, we can think that the reason why bronchoscopy can improve the prognosis of VAP patients is that whether it is aspiration of sputum or getting more accurate pathogens to help the adjustment of antibiotics, they all help to improve the inflammatory response of patients to some extent. Some scholars' study has shown that early bronchoscopy is associated with a lower 90days mortality rate in mechanically ventilated patients, which also supports our findings (Lee et al., 2015).

The results of the present subgroup analysis indicated no significant interaction between the subgroups regarding inhospital mortality, indicating that whether the ICU patient population with different characteristics underwent bronchial examination was consistent with the in-hospital mortality risk. Among the outcomes for ICU mortality, after bronchoscopy, patients with MI or CPD had a lower mortality risk than those who did not undergo bronchoscopy. When bronchoscopy is performed on patients in the ICU without LD, the mortality risk was lower than for those with LD. We will explain it step by step, chronic obstructive pulmonary disease and bronchiectasis are common chronic lung diseases chronic obstructive pulmonary disease and bronchiectasis are common chronic lung diseases (Raherison and Girodet, 2009; Hill et al., 2019), such patients are prone to infection and inflammation due to dysfunctional airway clearance and defense, and long-term chronic inflammation leads to bronchial epithelial cell degeneration, necrosis, bronchial scarring, distortion, impaired lung function, and sputum accumulation, which are more likely to occur in the presence of acute inflammation (Tantucci and Modina, 2012; Hill et al., 2019). There is research evidence that the hemodynamic changes in patients with MI will lead to varying degrees of pulmonary function changes (Hales and Kazemi, 1977), and there is a pathophysiological basis for the interaction between some chronic lung diseases and MI (Goedemans et al., 2020). Therefore, we can consider that when VAP is present, bronchoscopy is more likely to benefit in patients with chronic inflammatory disease of the lungs and varying degrees of changes in lung function. The liver can synthesize and remove most coagulation factors, plasminogen,

etc., and so LD can lead to coagulation and anticoagulation balance disorders (Amitrano et al., 2002; Monroe and Hoffman, 2009). One of the main complications of bronchoscopy is tracheal mucosal bleeding, so patients without LD are more likely to benefit from bronchoscopy than those with LD.

STRENGTHS AND LIMITATIONS

This research study was the first to explore the entire patients with VAP in the ICU from MIMIC-IV database, the large data sample provides a solid basis for the results. Furthermore, PSM and IPTW further confirmed the results. We also found that alterations in RDW mediated part of the positive effect of bronchoscopy on the prognosis of VAP patients by CMA methods. The technology for bronchoscopy is currently quite mature, and the results of this study provide evidence to support the guidance of clinicians for using this technique. Of course, our research still had certain limitations. First of all, because the specific diagnosis time of patients is not recorded in the analyzed database, this study cannot determine the duration between bronchoscopy and VAP, only how bronchoscopy impacts the prognoses of patients with VAP who received mechanical ventilation. Because of this we were also unable to analyze the specific antibiotics for VAP treatment, and so we did not consider the impact of antibiotic use on the outcome. Second, although we adopted multivariate analysis to control for confounding factors that may affect the results as much as possible, there are still potential confounding factors that cannot be corrected in a retrospective study. Finally, the interaction between subgroups needs to be analyzed prospective in a larger sample of people for further confirmation.

CONCLUSION

Bronchoscopy during MV was associated with reducing the risk of ICU and in-hospital mortality in patients with VAP in ICUs,

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and this beneficial effect was partially mediated by changes in RDW levels.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: The data were available on the MIMIC-IV website at https://mimic.physionet.org/, https://doi.org/10. 13026/a3wn-hq05.

AUTHOR CONTRIBUTIONS

LZ created the study protocol, performed the statistical analyses and wrote the first manuscript draft. SL conceived the study and wrote the first manuscript draft. SY assisted with manuscript revision and data confirmation. XL assisted with the study design. JiL assisted with data collection. YL and TH guided the literature review. JuL and HY conceptualized the research aims. All authors read and approved the final manuscript.

FUNDING

This work was supported by the National Natural Science Foundation of China (No. 82072232; 81871585), the Natural Science Foundation of Guangdong Province (No. 2018A030313058), Technology and Innovation Commission of Guangzhou Science, China (No. 201804010308), Guangdong Provincial Key Laboratory of Traditional Chinese Medicine Informatization (2021B1212040007).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.868920/full#supplementary-material

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GLOSSARY	VIF variance inflation factor
	IPTW propensity score-based inverse probability of treatment
AST aspartate aminotransferase	MCV mean corpuscular volume
ALT alanine aminotransferase	MCH mean corpuscular hemoglobin
AP alkaline phosphatase	MCHC mean corpuscular hemoglobin concentration
APSIII Acute Physiology Score III	MICU Medical Intensive Care Unit
AG anion gap	MIMIC Medical Information Mart for Intensive Care
BE base excess	MI myocardial infarction
BUN blood urea nitrogen	mHR mean heart rate
ACME average causal mediating effect	mMAP mean value of mean arterial pressure
ADE average direct effect	mRR mean respiratory rate
BMI body mass index	mT mean temperature
CRRT continuous renal replacement therapy	mSpO2 mean SpO2()
CHF congestive heart failure	PT prothrombin time
CD cerebrovascular disease	PTT partial thromboplastin time
CPD chronic pulmonary disease	PSM propensity score matching
LD liver disease	RD renal disease
CMA causal mediation analysis	RBC red blood cells
LDH lactate dehydrogenase	RDW red blood cell distribution width
IMV invasive mechanical ventilation	SICU Surgical Intensive Care Unit
ICU intensive care unit	NAD
INR international normalized ratio	VAP: ventilator-associated pneumonia
KM Kaplan-Meier	WBC white blood cells