Gender-and Age-based Differences in Outcomes of Mechanically Ventilated Patients in Intensive Care Units: A Chinese Multicentre Retrospective Study

Jia-Gui Ma
Fu Xing Hospital, Capital Medical University
Bo Zhu
Fu Xing Hospital, Capital Medical University
Li Jiang
Fu Xing Hospital, Capital Medcal University
Qi Jiang
Fu Xing Hospital, Capital Medical University
Xiu-Ming Xi (xxm2937@163.com)
Department of Critical Care Medicine, Fu Xing Hospital, Capital Medical University, Beijing 100038, China

Research

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Abstract

Background: Previous studies have suggested that the gender and/or age of a patient may influence clinical outcomes of critically ill patients. Our objective was to determine whether there are gender- and age-based differences in clinical outcomes for mechanically ventilated patients in intensive care units (ICUs).

Methods: We performed a multicentre retrospective study involving adult patients who were admitted to the ICU and received at least 24 hours of mechanical ventilation (MV). The patients were divided into two groups based on gender and, subsequently, further grouped based on gender and age $<$ or $\geq$ 65 years. The primary outcome measure was hospital mortality. Secondary outcome measures included duration of MV, hospital and ICU lengths of stay (LOS), and ICU mortality.

Results: A total of 853 mechanically ventilated patients were evaluated. Of those, 63.2% were men and 61.5% were $\geq$ 65 years of age. The hospital mortality rate for men was significantly higher than for women (35.4% vs. 28.7%, respectively; $p = 0.042$) and this difference was most pronounced among older patients (age $\geq$ 65 years; $p = 0.006$), even though there were no significant differences between both genders in age, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, type of admitting ICU, or in the number of comorbidities. We also found that the ICU mortality rate was significantly higher for men than for women among older patients ($p = 0.011$). However, the hospital and ICU mortality rates did not differ significantly between younger women and men. The durations of MV, ICU LOS, and hospital LOS was significantly longer for men than for women among younger patients ($p \leq 0.013$) but not among older patients. Multivariate logistic regression analysis revealed that gender was found to be independently associated with hospital mortality among the whole group of patients as well as older patients.

Conclusions: There were important gender- and age-based differences in outcomes among mechanically ventilated ICU patients. Our findings merit consideration when designing future clinical trials involving mechanically ventilated patients.

Introduction

Mechanical ventilation (MV) is one of the most commonly used treatment techniques in the intensive care unit (ICU). The proportion of patients receiving MV out of total ICU admissions has reached between 50% and 70% (1–5). With our aging population, the number of patients with MV will steadily increase, with a projected 80% increase by 2026 when compared to 2000 (6). Additionally, many studies have also shown that men account for more than half of patients receiving MV in the ICU (2, 3, 7–11). However, there have been few studies on the effect of gender on clinical outcomes in mechanically ventilated patients, and these results are inconsistent. Kollef et al (12) used multivariate analysis to show that women requiring mechanical ventilation were at greater risk for hospital mortality than men. In contrast, two other prospective studies showed that gender was not independently associated with hospital mortality (7, 10). It is not known whether these findings apply to other regions and patient populations. Our hypothesis is that there are significant differences in clinical outcomes between mechanically ventilated men and women, and that such gender-related differences may depend on age. To further investigate this hypothesis, we conducted a multicentre retrospective study of ICUs in Beijing.

Materials And Methods

Study Setting and Design

This retrospective observational cohort study was carried out in fourteen ICUs of thirteen tertiary teaching hospitals in Beijing between January 2012 and June 2013.

Among the fourteen participating ICUs, ten were medical-surgical ICUs, two were surgical ICUs, one was a respiratory ICU, and one was a medical ICU. The number of ICU beds ranged from eight to twenty during the study period. The research ethics board of each participating institution approved the study protocol with a waiver of informed consent.

Study Population

Patients who were admitted to the ICU and received at least 24 hours of invasive MV within the first 48 hours of ICU stay were eligible. Patients were excluded if they were less than 18 years old, had incomplete data sets, were diagnosed with neuromuscular disease, required chronic MV prior to hospital admission, or were transferred from other facilities and had already been intubated or tracheotomised. A patient was considered as one case if they were admitted to the ICU several times during the study period, and only data from the first ICU admission was analysed. In our study, older patients were defined as those ≥ 65 years of age at the time of hospital admission and the cohort was divided on the basis of gender and age (< or ≥ 65 years).

Data Collection

For every enrolled patient, the following data were recorded: demographic and epidemiological characteristics; type of admitting ICU; comorbidities; severity of illness; primary reason for MV; arterial blood gas measurements; MV parameters and settings; sedatives, analgesics, and neuromuscular blockers used during MV; total duration of MV; number of ventilator-free days; and the occurrence of successful weaning within 30 days; ICU and hospital lengths of stay (LOS); ICU and hospital costs; complications of MV; the occurrence of withholding or withdrawing life-sustaining treatments; and discharge destination. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score (13).

Outcomes of Interest

The primary outcome of interest was hospital mortality. Secondary outcomes included duration of MV, hospital and ICU LOS, and ICU mortality.

Statistical Analysis

Statistical analyses were carried out using SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as the mean ± standard deviation (SD) for normally distributed continuous variables, the median (interquartile range) for non-normally distributed variables, and the number (percentage) for categorical variables. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test. Multiple logistic regression with forward stepwise selection was used to determine risk factors of hospital mortality. Variables with a p value < 0.20 during univariate analysis as well as gender were entered into the multivariate analysis. To investigate how gender-related differences might depend on age, we prospectively chose 65 years of age as a cut-off and performed two separate multivariate analyses. A two-sided p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 853 mechanically ventilated patients were evaluated in this study. There were 539 men (63.2%) and 314 women (36.8%). There were 328 patients under the age of 65 years (38.5%) and 525 patients aged 65 years and older (61.5%). Baseline characteristics of the study population are shown in Table 1. Overall, there were no significant differences between both genders in age, body mass index (BMI), the need for non-invasive mechanical ventilation (NIMV) before ICU admission, type of admitting ICU, APACHE II score, or number of comorbidities. There was also no significant difference in the primary reason for MV between genders, except for trauma and coma. However, we found a significant difference in the proportion of men and women who had a history of smoking (50.3% vs. 9.6%, respectively; $p < 0.001$). Before the onset of mechanical ventilation, men tended to have a lower pulse oxygen saturation (SpO_2; $p = 0.032$).

Table 1

Baseline characteristics of mechanically ventilated ICU patients stratified by age and gender*

Variables	All women	All men		Women < 65 yr	Men < 65 yr		Women ≥ 65 year	Men ≥ 65 year	
	(n = 314)	(n = 539)	*p* value	(n = 120)	(n = 208)	*p* value	(n = 194)	(n = 331)	*p* value
Age (years)	72 (55, 79)	72 (55, 80)	0.546	49 (35, 58)	51 (41, 58)	0.298	78 (73, 82)	78 (73, 83)	0.356
BMI (kg/m^2)	23 (21, 26)	23 (21, 25)	0.156	23 (21, 26)	24 (21, 26)	0.799	23 (20, 26)	23 (21, 24)	0.057
History of smoking	30 (9.6)	271 (50.3)	< 0.001	6 (5.0)	112 (53.8)	< 0.001	24 (12.4)	159 (48.0)	< 0.001
Past history of surgery	82 (26.1)	133 (24.7)	0.641	35 (29.2)	52 (25.0)	0.410	47 (24.2)	81 (24.5)	0.950
NIMV before ICU admission	36 (11.5)	66 (12.2)	0.735	14 (11.7)	27 (13.0)	0.729	22 (11.3)	39 (11.8)	0.879
ICU admission source									
Medical ward	63 (20.1)	122 (22.6)	0.380	15 (12.5)	28 (13.5)	0.804	48 (24.7)	94 (28.4)	0.363
Surgical ward	145 (46.2)	252 (46.8)	0.871	64 (53.3)	113 (54.3)	0.862	81 (41.8)	139 (42.0)	0.957
Emergency department	97 (30.9)	150 (27.8)	0.342	34 (28.3)	60 (28.8)	0.921	63 (32.5)	90 (27.2)	0.198
Others	9 (2.9)	15 (2.8)	0.943	7 (5.8)	7 (3.4)	0.287	2 (1.0)	8 (2.4)	0.429
APACHE II score	15 (11, 21)	17 (11, 23)	0.227	12 (8, 18)	14 (8, 19)	0.568	18 (13, 24)	19 (13, 24)	0.376
Comorbidities									
Hypertension	156 (49.7)	247 (45.8)	0.277	28 (23.3)	49 (23.6)	0.963	128 (66.0)	198 (59.8)	0.160
Diabetes	99 (31.5)	134 (24.9)	0.035	16 (13.3)	26 (12.5)	0.828	83 (42.8)	108 (32.6)	0.020
Chronic renal failure	40 (12.7)	57 (10.6)	0.337	10 (8.3)	15 (7.2)	0.712	30 (15.5)	42 (12.7)	0.372

*Values given as No. (%) or MD (IQR).

ICU intensive care unit, *BMI* body mass index, *NIMV* non-invasive mechanical ventilation, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *COPD* chronic obstructive pulmonary disease, *MV* Mechanical ventilation, *ARDS* acute respiratory distress syndrome, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of carbon dioxide in arterial blood, SpO_2 pulse oxygen saturation, *MD* median, *IQR* interquartile range.

Variables	All women	All men		Women < 65 yr	Men < 65 yr		Women ≥ 65 year	Men ≥ 65 year	
Chronic heart failure	32 (10.2)	48 (8.9)	0.534	2 (1.7)	7 (3.4)	0.578	30 (15.5)	41 (12.4)	0.320
COPD	29 (9.2)	56 (10.4)	0.587	3 (2.5)	5 (2.4)	1.000	26 (13.4)	51 (15.4)	0.531
Cirrhosis	1 (0.3)	10 (1.9)	0.109	1 (0.8)	6 (2.9)	0.400	0 (0.0)	4 (1.2)	0.309
Pulmonary fibrosis	6 (1.9)	19 (3.5)	0.178	4 (3.3)	6 (2.9)	1.000	2 (1.0)	13 (3.9)	0.054
Cancer	35 (11.1)	69 (12.8)	0.476	11 (9.2)	15 (7.2)	0.528	24 (12.4)	54 (16.3)	0.220
Stroke	56 (17.8)	121 (22.4)	0.109	4 (3.3)	27 (13.0)	0.004	52 (26.8)	94 (28.4)	0.694
No. of comorbidities			0.592			0.590			0.053
None	91 (29.0)	174 (32.3)		70 (58.3)	112 (53.8)		21 (10.8)	62 (18.7)	
1	88 (28.0)	147 (27.3)		31 (25.8)	54 (26.0)		57 (29.4)	93 (28.1)	
≥ 2	135 (43.0)	218 (40.4)		19 (15.8)	42 (20.2)		116 (59.8)	176 (53.2)	
Primary reason for MV									
ARDS	30 (9.6)	47 (8.7)	0.682	16 (13.3)	16 (7.7)	0.907	14 (7.2)	31 (9.4)	0.396
Postoperative	127 (40.4)	195 (36.2)	0.215	58 (48.3)	100 (48.1)	0.964	69 (35.6)	95 (28.7)	0.101
Congestive heart failure	23 (7.3)	25 (4.6)	0.101	5 (4.2)	4 (1.9)	0.397	18 (9.3)	21 (6.3)	0.216
Aspiration	4 (1.3)	15 (2.8)	0.150	0 (0.0)	3 (1.4)	0.472	4 (2.1)	12 (3.6)	0.314
Pneumonia	49 (15.6)	111 (20.6)	0.072	11 (9.2)	28 (13.5)	0.247	38 (19.6)	83 (25.1)	0.150
Sepsis	14 (4.5)	34 (6.3)	0.258	7 (5.8)	15 (7.2)	0.631	7 (3.6)	19 (5.7)	0.277

*Values given as No. (%) or MD (IQR).

ICU intensive care unit, *BMI* body mass index, *NIMV* non-invasive mechanical ventilation, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *COPD* chronic obstructive pulmonary disease, *MV* Mechanical ventilation, *ARDS* acute respiratory distress syndrome, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of carbon dioxide in arterial blood, SpO_2 pulse oxygen saturation, *MD* median, *IQR* interquartile range.

Variables	All women	All men		Women < 65 yr	Men < 65 yr		Women ≥ 65 year	Men ≥ 65 year	
Trauma	0 (0.0)	11 (2.0)	0.026	0 (0.0)	9 (4.3)	0.050	0 (0.0)	2 (0.6)	0.533
Cardiac arrest	10 (3.2)	17 (3.2)	0.980	2 (1.7)	6 (2.9)	0.751	8 (4.1)	11 (3.3)	0.636
COPD or asthma	17 (5.4)	33 (6.1)	0.671	1 (0.8)	3 (1.4)	1.000	16 (8.2)	30 (9.1)	0.750
Chronic pulmonary disease	7 (2.2)	10 (1.9)	0.706	5 (4.2)	3 (1.4)	0.242	2 (1.0)	7 (2.1)	0.565
Coma	22 (7.0)	18 (3.3)	0.015	9 (7.5)	10 (4.8)	0.315	13 (6.7)	8 (2.4)	0.016
Other	11 (3.5)	23 (4.3)	0.582	6 (5.0)	11 (5.3)	0.910	5 (2.6)	12 (3.6)	0.513
Arterial blood gas analysis prior to MV									
pH	7.36 (7.25, 7.42)	7.36 (7.25, 7.42)	0.885	7.38 (7.29, 7.44)	7.36 (7.25, 7.42)	0.162	7.34 (7.23, 7.40)	7.35 (7.25, 7.42)	0.200
PaO_2/FiO_2	183 (120, 285)	168 (112–273)	0.412	194 (117, 319)	181 (118–314)	0.941	180 (120, 248)	160 (110–255)	0.268
$PaCO_2$ (mmHg),	40 (33, 52)	40 (34, 52)	0.790	36 (32, 42)	39 (33, 47)	0.112	42 (34, 64)	41 (34, 56)	0.359
SpO_2 (%)	95 (89, 100)	95 (88, 99)	0.032	97 (89, 100)	95 (90, 99)	0.142	95 (89, 99)	93 (88, 98)	0.100

*Values given as No. (%) or MD (IQR).

ICU intensive care unit, *BMI* body mass index, *NIMV* non-invasive mechanical ventilation, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *COPD* chronic obstructive pulmonary disease, *MV* Mechanical ventilation, *ARDS* acute respiratory distress syndrome, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of carbon dioxide in arterial blood, SpO_2 pulse oxygen saturation, *MD* median, *IQR* interquartile range.

Management of **mechanically ventilated ICU patients**

Table 2 shows the data related to mechanically ventilated patient management, which is stratified by age and gender. There was a significant difference in the tidal volume (VT) between men and women ($p < 0.001$), which remained significant even after stratification by age ($p < 0.001$). The incidence rates of ventilator-associated pneumonia (VAP) and tracheostomy in both men and women were high, but the incidence rate of self-extubation was low. Among the younger age group (< 65 years), we found that the incidence rates of VAP and tracheostomy were significantly higher among men than among women. However, there was no significant difference in these rates among the older age group (≥ 65 years). No differences were found between men and women in the choice of mechanical ventilation mode, the use of positive end-expiratory pressure (PEEP); or the use of sedatives, analgesics and neuromuscular blockers.

Table 2

Management of mechanical ventilation in ICU patients stratified by age and gender*

Variables	All women	All men		Women < 65 yr	Men < 65 yr		Women ≥ 65 year	Men ≥ 65 year	
	(n = 314)	(n = 539)	*p* value	(n = 120)	(n = 208)	*p* value	(n = 194)	(n = 331)	*p* value
Mode and parameter setting at the beginning of MV									
Mode of MV			0.099			0.375			0.055
VCV	76 (24.2)	99 (18.4)		32 (26.7)	39 (18.8)		44 (22.7)	60 (18.1)	
PCV	28 (8.9)	72 (13.4)		11 (9.2)	20 (9.6)		17 (8.8)	52 (15.7)	
PSV	73 (23.2)	111 (20.6)		27 (22.5)	46 (22.1)		46 (23.7)	65 (19.6)	
SIMV	19 (6.1)	27 (5.0)		5 (4.2)	15 (7.2)		14 (7.2)	12 (3.6)	
SIMV + PSV	113 (36.0)	223 (41.4)		42 (35.0)	86 (41.3)		71 (36.6)	137 (41.4)	
Others	5 (1.6)	7 (1.3)		3 (2.5)	2 (1.0)		2 (1.0)	5 (1.5)	
Ventilator's parameter setting									
VT (ml/kg predicted bodyweight)	8.20 (7.38, 8.88)	6.77 (6.07, 7.45)	< 0.001	8.25 (7.38, 9.01)	6.83 (6.32, 7.59)	< 0.001	8.07 (7.38, 8.70)	6.68 (6.07, 7.37)	< 0.001
Applied PEEP (cmH_2O)	5 (5, 8)	6 (5, 8)	0.298	5 (5, 8)	6 (5, 8)	0.617	6 (5, 8)	6 (5, 8)	0.339
Peak pressure (cmH_2O)	24 (20, 28)	24 (20, 28)	0.604	24 (20, 27)	24 (19, 28)	0.702	24 (20, 28)	24 (20, 29)	0.350
Plateau pressure (cmH_2O)	17 (13, 21)	18 (14, 20)	0.759	18 (14, 21)	18 (13, 20)	0.634	17 (12, 21)	18 (14, 22)	0.472
Use of sedatives,	258 (82.2)	452 (83.9)	0.523	104 (86.7)	176 (84.6)	0.613	154 (79.4)	276 (83.4)	0.250

*Values given as No. (%) or MD (IQR).

ICU intensive care unit, *MV* Mechanical ventilation, *VCV* volume-control ventilation, *PCV* pressure-control ventilation, *SIMV* synchronized intermittent mandatory ventilation, *PSV* pressure support ventilation, *VT* tidal volume, *PEEP* positive end-expiratory pressure, *VAP* ventilator-associated pneumonia, *PMV* prolonged mechanical ventilation, *MD* median, *IQR* interquartile range.

[a] Barotrauma refers to the development of at least one of the following: interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum or subcutaneous emphysema.

[b] PMV was defined as the need for mechanical ventilation for more than 21 days.

Variables	All women	All men		Women < 65 yr	Men < 65 yr		Women ≥ 65 year	Men ≥ 65 year	
Use of analgesics	196 (62.4)	334 (62.0)	0.895	90 (75.0)	149 (71.6)	0.509	106 (54.6)	185 (55.9)	0.781
Use of neuromuscular blockers	11 (3.5)	23 (4.3)	0.582	5 (4.2)	8 (3.8)	1.000	6 (3.1)	15 (4.5)	0.417
Complications of MV									
Barotrauma [a]	8 (2.5)	6 (1.1)	0.112	4 (3.3)	3 (1.4)	0.456	4 (2.1)	3 (0.9)	0.472
VAP	51 (16.2)	103 (19.1)	0.294	9 (7.5)	34 (16.3)	0.022	42 (21.6)	69 (20.8)	0.828
Self-extubation	5 (1.6)	5 (0.9)	0.589	1 (0.8)	1 (0.5)	1.000	4 (2.1)	4 (1.2)	0.688
Reintubation	21 (6.7)	24 (4.5)	0.159	5 (4.2)	5 (2.4)	0.575	16 (8.2)	19 (5.7)	0.266
Tracheotomy	44 (14.0)	93 (17.3)	0.214	13 (10.8)	40 (19.2)	0.047	31 (16.0)	53 (16.0)	0.992
PMV [b]	37 (11.8)	71 (13.2)	0.556	6 (5.0)	22 (10.6)	0.082	31 (16.0)	49 (14.8)	0.717

*Values given as No. (%) or MD (IQR).

ICU intensive care unit, *MV* Mechanical ventilation, *VCV* volume-control ventilation, *PCV* pressure-control ventilation, *SIMV* synchronized intermittent mandatory ventilation, *PSV* pressure support ventilation, *VT* tidal volume, *PEEP* positive end-expiratory pressure, *VAP* ventilator-associated pneumonia, *PMV* prolonged mechanical ventilation, *MD* median, *IQR* interquartile range.

[a] Barotrauma refers to the development of at least one of the following: interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum or subcutaneous emphysema.

[b] PMV was defined as the need for mechanical ventilation for more than 21 days.

Clinical outcomes

As shown in Table 3, the duration of MV, ICU LOS, and hospital LOS were significantly longer for men than for women among the younger age group ($p \leq 0.013$), but no significant differences were observed in these times among the older age group.

Table 3

Outcomes of mechanically ventilated ICU patients stratified by age and gender*

Variables	All women	All men		Women < 65 yr	Men < 65 yr		Women ≥ 65 year	Men ≥ 65 year	
	(n = 314)	(n = 539)	*p* value	(n = 120)	(n = 208)	*p* value	(n = 194)	(n = 331)	*p* value
Ventilator-free days within 30 days [a] (days)	23 (0, 27)	20 (0, 27)	0.025	26 (1, 28)	24 (9, 27)	0.258	19 (0, 27)	11 (0, 26)	0.024
Successful weaning within 30 days [b]	202 (64.3)	320 (59.4)	0.151	86 (71.7)	154 (74.0)	0.641	116 (59.8)	166 (50.2)	0.032
Total duration of MV(hrs)	104 (46, 236)	136 (60, 287)	0.008	73 (41, 160)	112 (58, 237)	0.003	125 (56, 339)	154 (64, 328)	0.255
ICU LOS (days)	7 (4, 15)	9 (5, 19)	0.001	5 (3, 10)	8 (4, 16)	< 0.001	9 (4, 20)	11 (5, 21)	0.173
Hospital LOS (days)	21 (12, 35)	24 (14, 40)	0.015	19 (11, 36)	25 (14, 40)	0.013	21 (13, 35)	24 (14, 40)	0.252
ICU mortality	85 (27.1)	178 (33.0)	0.069	24 (20.0)	37 (17.8)	0.620	61 (31.4)	141 (42.6)	0.011
Hospital mortality	90 (28.7)	191 (35.4)	0.042	25 (20.8)	40 (19.2)	0.726	65 (33.5)	151 (45.6)	0.006
ICU costs (10000 CNY)	5.5 (2.7, 10.9)	7.3 (3.7, 14.7)	< 0.001	4.4 (2.1, 7.9)	6.7 (3.3, 12.5)	< 0.001	7.2 (3.5, 13.4)	7.8 (4.1, 15.5)	0.067
Hospital costs (10000 CNY)	9.9 (5.5, 15.5)	12.0 (7.2, 19.9)	< 0.001	7.3 (4.2, 13.1)	11.9 (6.8, 20.3)	< 0.001	10.9 (5.9, 16.7)	12.1 (7.2, 19.9)	0.041
Withhold/withdraw life sustaining treatments	47 (15.0)	82 (15.2)	0.914	14 (11.7)	24 (11.5)	0.972	33 (17.0)	58 (17.6)	0.869
Discharge destination			0.010			0.030			0.290

*Values given as No. (%) or MD (IQR).

ICU intensive care unit, *MV* Mechanical ventilation, *LOS* length of stay, *CNY* Chinese yuan, *MD* median, *IQR* interquartile range.

[a] Ventilator-free days within 30 days are defined as 30 minus the total number of days with invasive MV. Non-survivors were considered as having 0 ventilator-free days.

[b] Successful weaning from MV was defined as complete respiratory autonomy for at least 48 h.

Variables	All women	All men	Women < 65 yr	Men < 65 yr	Women ≥ 65 year	Men ≥ 65 year
Home	195 (87.1)	265 (76.1)	83 (87.4)	124 (73.8)	112 (86.8)	141 (78.3)
Respiratory care ward	8 (3.6)	15 (4.3)	3 (3.2)	5 (3.0)	5 (3.9)	10 (5.6)
Nursing home	3 (1.3)	10 (2.9)	0 (0.0)	2 (1.2)	3 (2.3)	8 (4.4)
Other hospital	18 (8.0)	58 (16.7)	9 (9.5)	37 (22.0)	9 (7.0)	21 (11.7)

*Values given as No. (%) or MD (IQR).

ICU intensive care unit, *MV* Mechanical ventilation, *LOS* length of stay, *CNY* Chinese yuan, *MD* median, *IQR* interquartile range.

[a] Ventilator-free days within 30 days are defined as 30 minus the total number of days with invasive MV. Non-survivors were considered as having 0 ventilator-free days.

[b] Successful weaning from MV was defined as complete respiratory autonomy for at least 48 h.

Despite the observation that men and women 65 years or older had similar severities upon ICU admission, mortality was higher among men than among women in the ICU (42.6% vs. 31.4%, respectively; $p = 0.011$) and in the hospital (45.6% v. 33.5%, respectively; $p = 0.006$) (Table 3). Mortality rates did not differ significantly between younger men and women.

In the overall study population as well as in both age groups, men had higher hospital and ICU costs than women. There was no significant difference in the occurrence of withholding or withdrawing life-sustaining treatments between men and women in the overall study population and in both age groups. Overall, the proportion of women who were directly discharged to home was higher than that of men.

Multivariate logistic regression analyses

Using multivariate logistic regression analysis, we found that age, gender, type of admitting ICU (medical ward), APACHE II score, hospital LOS, the presence of complications of MV, and the decision to withhold or withdraw life-sustaining treatments were independently associated with hospital mortality in the overall study population (Table 4).

Table 4
Multivariate logistic regression analysis of factors independently associated with hospital mortality

Factors	All patients (n = 853)		< 65 years (n = 328)		≥ 65 years (n = 525)	
	AOR (95% CI)	*P* value	AOR (95% CI)	*P* value	AOR (95% CI)	*P* value
Age (years)	1.026 (1.014–1.039)	< 0.001	1.013 (0.986–1.040)	0.356	1.062 (1.030–1.096)	< 0.001
Male gender	1.611 (1.101–2.356)	0.014	0.879 (0.446–1.731)	0.709	2.074 (1.315–3.269)	0.002
ICU admission source: Medical ward	1.650 (1.092–2.493)	0.018	2.330 (0.993–5.464)	0.052	1.393 (0.864–2.245)	0.174
APACHE II score	1.079 (1.055–1.105)	< 0.001	1.080 (1.038–1.124)	< 0.001	1.096 (1.066–1.127)	< 0.001
Hospital LOS (days)	0.984 (0.977–0.992)	< 0.001	0.995 (0.982–1.008)	0.446	0.986 (0.978–0.994)	< 0.001
Complications of MV						
Barotrauma [a]	10.613 (2.942–38.285)	< 0.001	14.561 (2.619–80.957)	0.002	9.075 (1.530–53.820)	0.015
VAP	1.763 (1.103–2.819)	0.018	2.199 (0.916–5.281)	0.078	2.004 (1.182–3.397)	0.010
Reintubation	2.271 (1.028–5.021)	0.043	1.974 (0.396–9.849)	0.407	2.541 (1.052–6.133)	0.038
PMV [b]	1.869 (1.047–3.335)	0.034	2.543 (0.974–6.640)	0.057	1.493 (0.754–2.956)	0.250
Withhold/withdraw life sustaining treatments	10.928 (6.629–18.016)	< 0.001	17.021 (7.617–38.037)	< 0.001	9.715 (5.212–18.109)	< 0.001

AOR adjusted odds ratio, *CI* confidence *interval*, *ICU* intensive care unit, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *LOS* length of stay, *MV* Mechanical ventilation, *VAP* ventilator-associated pneumonia, *PMV* prolonged mechanical ventilation.

[a] Barotrauma refers to the development of at least one of the following: interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum or subcutaneous emphysema.

[b] PMV was defined as the need for mechanical ventilation for more than 21 days.

In order to study if gender-related differences might depend on age, we prospectively chose a cut-off value of 65 years of age. Therefore, we used separate models for patients less than 65 years old and for those 65 years or older. We found that the male gender was not independently associated with hospital mortality among patients less than 65 years. However, after adjusting for all other factors, we found that the male gender was independently associated with hospital mortality among older patients (adjusted odds ratio [AOR] = 2.074; 95% confidence interval [CI] = 1.315 to 3.269; $p = 0.002$), as shown in Table 4. Multiple logistic regression analysis also demonstrated that patient age was independently associated with hospital mortality among older patients.

Discussion

We conducted a multicentre retrospective study to evaluate the clinical characteristics and outcomes in mechanically ventilated patients according to gender and age. The main finding of this study was that gender- and age-related differences in clinical outcomes among mechanically ventilated patients exist. More importantly, we found that the male gender was independently associated with hospital mortality in the overall study population as well as among patients 65 years or older but not among patients less than 65 years old.

As reported in other studies (2, 3, 7–11), we found that men account for more than half of patients (63.2%) receiving mechanical ventilation in the ICU. These findings are even more surprising when we consider the gender distribution of the Chinese urban adult population. For example, in 2010, women accounted for nearly 50% of the Chinese urban adult population, and this proportion increased with age (14). It is not clear why the proportion of women receiving mechanical ventilation in the ICU is generally lower than that of men, but this may be due to differences in treatment preferences or gender bias. Women were less likely than men to be admitted to an ICU and to receive care and life-supporting treatments such as mechanical ventilation, despite the fact that the severity of illness was similar in men and women or even higher in women (3, 15–18). This difference in care may stem from less aggressive treatment preferences by women (or their surrogates) (16, 19, 20). Men preferred life-sustaining treatments more than women overall, for specific treatments, and in response to specific health scenarios. Furthermore, Sagy et al (21) reported that having the female gender of both the physician and the patient was associated with a decreased ICU admission rate of critically ill patients. Their findings indicated the existence of possible gender bias where having the female gender of the patient and the treating physician diminish the likelihood of restricted health resource use.

In this study we found that the overall hospital mortality rate for men was greater than the overall hospital mortality rate for women (35.4% vs 28.7%, respectively; $p = 0.042$), despite similar age, the severity of illness, type of admitting ICU, and the number of comorbidities between both genders. When we analysed the overall study population according to age (< or ≥ 65 years) and gender, in the younger age group, despite the fact that the duration of MV, ICU LOS and hospital LOS were significantly longer for men than for women, we found that the ICU and hospital mortality rates were slightly higher for women than for men (20.0% vs.17.8% in the ICU and 20.8% vs.19.2% in the hospital, respectively), although these differences were not statistically significant. However, in the group of those 65 years or older who had similarities in age, severity of illness, type of admitting ICU, and the number of comorbidities, we found statistically significant differences in ICU and hospital mortality rates according to gender ($p \leq 0.011$). The ICU and hospital mortality rates were significant higher for men than for women. In addition, using multiple logistic regression analysis, we found that gender had no effect of among the younger age group. However, among the older age group, after adjusting for all other factors, we found that the male gender was independently associated with hospital mortality ($p = 0.002$). Therefore, the results of this study demonstrated that there were gender- and age-related differences in clinical outcomes among mechanically ventilated ICU patients. We believe that there may be an interaction between age and gender, and that this interaction usually intensifies with age. The association of old age and male gender may be strongly related to mortality in mechanically ventilated ICU patients.

Although previous studies have explored the effects of gender on the outcomes of mechanically ventilated ICU patients, the findings across these studies are often inconsistent (7, 10, 12). Our results are also inconsistent with or even contrary to these previous studies. Possible reasons for this inconsistency is that two of the three studies did not further explore the effect of the interaction between age and gender on the outcome of mechanically ventilated patients, the mean age of patients included in the three studies was significantly different, and all patients studied were less than 65 years old. Age has been shown to be independently associated with mortality in mechanically ventilated ICU patients, and this correlation increases with age (5, 7, 12). Our study also supports this finding. Moreover, Fowler et al (3) found that sex- and age-related differences exist among ICU admissions, receipt of specific life-supporting interventions, and in short- and long-term outcomes. Mahmood et al (17) also found that there was a statistically significant interaction between gender and age among critically ill patients. Women less than 50 years of age had a lower ICU mortality rate compared to men, while women 50 years of age or older did not have a significant difference when compared to men. Therefore, when evaluating the effect of gender on the outcome of mechanically ventilated patients, we should not ignore the age-related effect. Another possible reason for this inconsistency may be due to referral bias or differences in the composition of ICU admission diagnoses. In previous studies, mechanically ventilated patients were either all medical patients (10), mainly medical patients (7), or half medical and half surgical patients (12). In this study, among the younger age group, more than half of the mechanically ventilated patients came from the surgical ward, while in the older age group, this proportion decreased significantly. Compared with women, men were more frequently admitted to the ICU from both the medical ward and surgical ward, although the difference was not significant. In the study by Reinikainen et al., male gender was found to be independently associated with increased hospital mortality among postoperative patients and among patients aged 75 years or older but not among medical patients (22). Women had a higher mortality compared to men after coronary artery bypass graft surgery and lower mortality with COPD exacerbation. There was no difference in mortality in acute coronary syndrome, sepsis, or trauma among the critically ill patients (17).

Our findings confirmed that there were gender- and age- related differences in mortality among mechanically ventilated ICU patients, but the reasons for these differences are poorly understood. When investigating the outcome of critically ill patients, in addition to considering age, hormonal status is also an important factor. In numerous clinical and experimental studies, sex hormones have been shown to affect gender-specific immune responses and organ functions after shock, trauma, and sepsis. Specifically, studies indicate that female hormones are protective in both immune responses and organ functions, whereas male sex hormones are deleterious (23–26). In fact, the inflammatory response to infection seems exacerbated in males, as compared with females (27). The available information indicates that sex hormones play a key role in regulating immune response and organ function. In addition, there were gender differences in neuroendocrine and endothelial responses in critically ill patients, possibly mediated or regulated by sex hormones (26). Thus, differences in the hormonal status of critically ill patients may partly explain the gender-related differences in the rate of disease progression and response to treatment in ICU patients. In our study, we found that the duration of MV, ICU LOS and hospital LOS were significantly longer for men than for women both in the overall study population and in different age subgroups. These results imply that women may be more capable of recovering from critical illness or surgery than men. However, despite sex hormones playing a very important role, it is not enough to comprehensively account for the gender differences in the clinical outcomes of critically ill patients.

In an international multicentre prospective study, Esteban et al (7) used multivariate analysis to show that the main conditions independently associated with increased mortality in mechanically ventilated ICU patients included not only the factors present at the start of MV (such as age, prior functional status, etc.), but also factors related to patient management (such as having a plateau pressure > 35 cmH_2O, tracheostomy, etc.) and factors that developed during MV (such as barotrauma, organ failures, etc.). Similarly, in our study we found that in the overall study population, the type of admitting ICU, APACHE II score, hospital LOS, presence of complications of MV, and withholding or withdrawing of life-sustaining treatments were also independently associated with hospital mortality. However, our study showed that differences in baseline characteristics and management of MV in male and female patients did not seem to be significant, so these factors did not seem to explain the differences in mortality between males and females.

To the best of our knowledge, this is the first multicentre retrospective study in China providing data that indicate gender- and age-related differences in clinical outcomes among mechanically ventilated ICU patients. However, we also are aware of several limitations of our study. First, this study is a retrospective study, and the data were obtained between 2012–2013, which may impose temporal limitations on the applicability of this data set. Second, the 14 ICUs included in our study population are all in Beijing, and these ICUs may not be representative of a random sample of Chinese ICUs. Thus, our research results may not be applicable to other regions or countries. Third, our study did not include other important variables, including nutritional status, degree of organ dysfunction, and other invasive procedures, which may also account for gender differences in outcomes. The effect of gender on the outcomes of critically ill patients is complex, and the underlying mechanisms remain unclear. Therefore, it is necessary to conduct more prospective studies, specifically designed to address gender differences and their underlying mechanisms; hormonal status should also be examined.

Conclusion

In the present study, we demonstrate the existence of gender- and age-related differences in clinical outcomes among mechanically ventilated ICU patients. The male gender was found to be independently associated with increased hospital mortality in the overall study population and among patients 65 years or older but not among patients less than 65 years old. In addition, male patients were treated longer than female patients. We believe that there may be an interaction between age and gender, and that this interaction usually intensifies with age. Our findings merit consideration when designing future clinical trials involving mechanically ventilated patients.

Abbreviations

MV
Mechanical ventilation; ICU:Intensive care unit; LOS:Length of stay; APACHE:Acute Physiology and Chronic Health Evaluation; SD:Standard deviation; IQR:Interquartile range; MD, median; BMI:Body mass index; NIMV:Non-invasive mechanical ventilation; COPD:Chronic obstructive pulmonary disease; NYHA:New York Heart Association; ARDS:Acute respiratory distress syndrome; PaO_2:Partial pressure of oxygen in arterial blood; FiO_2:Fraction of inspired oxygen; $PaCO_2$:Partial pressure of carbon dioxide in arterial blood; SpO_2:Pulse oxygen saturation; VCV:Volume-control ventilation; PCV:Pressure-control ventilation; PSV:Pressure support ventilation;

SIMV:Synchronized intermittent mandatory ventilation; VT; Tidal volume; PEEP:Positive end-expiratory pressure; VAP:Ventilator-associated pneumonia; PMV:Prolonged mechanical ventilation; CNY:Chinese yuan; AOR:Adjusted odds ratio; CI:Confidence interval.

Declarations

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Authors' contributions:

JM contributed to the study conception and design, data and statistical analysis, and manuscript preparation. BZ, LJ, QJ contributed to study design, data analysis, and manuscript revision. XX contributed to the study conception and design, data and statistical analysis, manuscript revision and supervision of the study. All authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

References

1. Du B, An Y, Kang Y, Yu X, Zhao M, Ma X, et al. Characteristics of critically ill patients in ICUs in mainland China. Crit Care Med. 2013;41(1):84–92.
2. Metnitz PG, Metnitz B, Moreno RP, Bauer P, Del Sorbo L, Hoermann C, et al. Epidemiology of mechanical ventilation: analysis of the SAPS 3 database. Intensive Care Med. 2009;35(5):816–25.

3. Fowler RA, Sabur N, Li P, Juurlink DN, Pinto R, Hladunewich MA, et al. Sex-and age-based differences in the delivery and outcomes of critical care. CMAJ. 2007;177(12):1513–9.
4. Sacanella E, Perez-Castejon JM, Nicolas JM, Masanes F, Navarro M, Castro P, et al. Mortality in healthy elderly patients after ICU admission. Intensive Care Med. 2009;35(3):550–5.
5. Farfel JM, Franca SA, Sitta Mdo C, Filho WJ, Carvalho CR. Age, invasive ventilatory support and outcomes in elderly patients admitted to intensive care units. Age Ageing. 2009;38(5):515–20.
6. Needham DM, Bronskill SE, Calinawan JR, Sibbald WJ, Pronovost PJ, Laupacis A. Projected incidence of mechanical ventilation in Ontario to 2026: Preparing for the aging baby boomers. Crit Care Med. 2005;33(3):574–9.
7. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. Jama. 2002;287(3):345–55.
8. Ye Y, Zhu B, Jiang L, Jiang Q, Wang M, Hua L, et al. A Contemporary Assessment of Acute Mechanical Ventilation in Beijing: Description, Costs, and Outcomes. Crit Care Med. 2017;45(7):1160–7.
9. Esteban A, Anzueto A, Frutos-Vivar F, Alia I, Ely EW, Brochard L, et al. Outcome of older patients receiving mechanical ventilation. Intensive Care Med. 2004;30(4):639–46.
10. Epstein SK, Vuong V. Lack of influence of gender on outcomes of mechanically ventilated medical ICU patients. Chest. 1999;116(3):732–9.
11. Esteban A, Anzueto A, Alia I, Gordo F, Apezteguia C, Palizas F, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med. 2000;161(5):1450–8.
12. Kollef MH, O'Brien JD, Silver P. The impact of gender on outcome from mechanical ventilation. Chest. 1997;111(2):434–41.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
14. National Bureau of Statistics of China. The 2010 population census of the People's Republic of China. http://www.stats.gov.cn/tjsj/pcsj/rkpc/6rp/indexch.htm (in Chinese). Accessed April 10, 2020.
15. Valentin A, Jordan B, Lang T, Hiesmayr M, Metnitz PG. Gender-related differences in intensive care: a multiple-center cohort study of therapeutic interventions and outcome in critically ill patients. Crit Care Med. 2003;31(7):1901–7.
16. Sharma RK, Prigerson HG, Penedo FJ, Maciejewski PK. Male-female patient differences in the association between end-of-life discussions and receipt of intensive care near death. Cancer. 2015;121(16):2814–20.
17. Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. Crit Care. 2012;16(3):R92.
18. Shen HN, Lu CL, Yang HH. Women receive more trials of noninvasive ventilation for acute respiratory failure than men: a nationwide population-based study. Crit Care. 2011;15(4):R174.
19. Bookwala J, Coppola KM, Fagerlin A, Ditto PH, Danks JH, Smucker WD. Gender differences in older adults' preferences for life-sustaining medical treatments and end-of-life values. Death Stud. 2001;25(2):127–49.
20. Nakamura K, Kinugasa Y, Sugihara S, Hirai M, Yanagihara K, Haruki N, et al. Sex differences in surrogate decision-maker preferences for life-sustaining treatments of Japanese patients with heart failure. ESC heart failure. 2018;5(6):1165–72.

21. Sagy I, Fuchs L, Mizrakli Y, Codish S, Politi L, Fink L, et al. The association between the patient and the physician genders and the likelihood of intensive care unit admission in hospital with restricted ICU bed capacity. QJM. 2018;111(5):287–94.
22. Reinikainen M, Niskanen M, Uusaro A, Ruokonen E. Impact of gender on treatment and outcome of ICU patients. Acta anaesthesiologica Scandinavica. 2005;49(7):984–90.
23. Yu HP, Chaudry IH. The role of estrogen and receptor agonists in maintaining organ function after trauma-hemorrhage. Shock. 2009;31(3):227–37.
24. Angele MK, Schwacha MG, Ayala A, Chaudry IH. Effect of gender and sex hormones on immune responses following shock. Shock. 2000;14(2):81–90.
25. Angele MK, Pratschke S, Chaudry IH. Does gender influence outcomes in critically ill patients? Critical care. (London England). 2012;16(3):129-.
26. Papathanassoglou ED, Middleton N, Hegadoren K. Sex-dependent disparities in critical illness: methodological implications for critical care research. Nurs Crit Care. 2015;20(2):58–62.
27. Mathieu C, Leone M. Gender and sepsis: first step of personalized medicine? Minerva Anestesiol. 2018;84(4):434–6.