

The effect of loop diuretics on 28-day mortality of patients with acute respiratory distress syndrome

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Research

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Abstract

Background Diuretics have been widely used in critically ill patients while it remains uncertain whether it could reduce mortality of patients with acute respiratory distress syndrome (ARDS). The study aimed to investigate the association between diuretics and 28-day mortality of ARDS patients.

Methods This is a secondary analysis of the NHLBI ARDS Network's FACTT. Patients enrolled in FACTT who did not receive renal replacement therapy within the first 48 hours after enrollment were included. Marginal structural Cox model (MSCM) was used to investigate any association between diuretics and 28-day mortality after correction of both baseline and time-fixed variables. Latent class model (LCA) and subgroup analysis were performed to detect which kind of patients could benefit from diuretics.

Results In total, 932 patients were enrolled including 558 in the diuretics group and 374 in the no diuretics group within the first 48 hours. The 28-day mortality was lower in the diuretics group (15.1% vs. 28.1%, $p < 0.001$). MSCM revealed that diuretics use was related to an improved 28-day mortality (HR 0.78; 95%CI 0.62–0.99; $p = 0.04$). LCA identified three subtypes, and diuretics were associated with reduced mortality in subtype3, which were characterized by worse renal function and higher CVP. Subgroup analysis indicated survival advantage among patients who are female, sepsis induced ARDS, and those with $\text{PaO}_2/\text{FiO}_2 \leq 150$ mmHg, $\text{MAP} \geq 65$ mmHg.

Conclusion Loop diuretics are associated with reduced 28-day mortality of ARDS patients, after controlling for time-varying confounders. Randomized trials are required to verify the results.

Introduction

Acute respiratory distress syndrome which results from various insults is associated with a high hospital mortality of 40%^[1]. The hallmark alteration of ARDS is increased endothelial and epithelial permeability, leading to increased extravascular lung water (EVLW)^[2], which correlates with lung injury and mortality^[3]. Diuretics, which have been frequently administered in the critically ill to alleviate pulmonary edema may reduce lung injury theoretically^[4].

Several studies have involved diuretics as part of therapeutic intervention for ARDS, but whether it could reduce mortality is non-conclusive. Diuretics have been found to be associated with decreased positive fluid balance, improved lung function and shorter mechanical ventilation duration, but no mortality improvement has been detected^[5, 6]. Although, a retrospective study suggested that diuretic use in 48 to 72 h after meeting ARDS criteria might reduce mortality^[7]. The influence of diuretics use beyond the specified 24 hours and changes in treatment related to diuretics were not analyzed, which makes the result less explicable.

The controversial results may due to the following reasons. First, ARDS is of enormous heterogeneity and patients with diverse phenotypes response variously to the selected treatment^[8–10]. In addition, the use of diuretics is a time-dependent variable, depending on factors such as oxygenation and mean arterial

pressure (MAP), while these confounders were seldom corrected and hence leading to bias. Previous study found that after adjusting for baseline variables only, diuretics were associated with lower 28-day mortality in critically ill patients. However, when time-varying confounders were corrected by MSCM, no association was detected^[11]. The research highlighted the necessity to consider the time-dependent variables when investigating the effect of diuretics on patient outcomes.

Diuretics are widely used in the critically ill, despite controversies exist on whether it could reduce mortality. The present study aimed to evaluate the effect of loop diuretics on 28-day mortality of ARDS patients, using marginal structural model to adjust time-varying variables. We hypothesized that diuretics would improve 28-day mortality of patients with ARDS. LCA was applied to derive phenotypes, and subgroup analysis was conducted to determine which phenotype may benefit from diuretics.

Methods

Study design and population

The study was a secondary analysis of the NHLBI ARDS Network's FACTT (Fluid and Catheter Treatment Trial). Details of the trial have been published^[5, 12]. In the original study, ARDS patients receiving mechanical ventilation were included. Exclusion criteria were with ARDS for more than 48 hours, chronic diseases which impair survival and weaning. We further excluded patients receiving renal replacement therapy routinely or within the first 48 hours after enrollment, to whom diuretics were not likely to be prescribed.

The fluid management strategies were carried out for seven days from randomization, or until weaning, whichever occurred first. Furosemide or other substituted diuretics were administered in patients with elevated central venous pressure (CVP) or pulmonary arterial wedge pressure (PAWP) when hemodynamics was stable. Patients were divided into two groups according to whether they received diuretics within the first 48 hours. The need for informed consent was waived. The primary outcome was the 28-day mortality.

Data collection

The following variables were extracted: demographic data, comorbidities, laboratory tests, Acute Physiology and Chronic Health Evaluation III score, prescriptions of vasopressor or diuretics. Sequential Organ Failure Assessment score, Charlson Comorbidity Index^[13], Murray lung injury score^[14] were calculated. The number of missing or censoring values was presented in Table S1. Variables with a missing ratio of more than 25% were not included in the final analysis. Outliers were censored and missing values were replaced by multiple imputations.

Statistical analysis

Continuous variables were presented as mean (standard deviation) or median (interquartile ranges) and compared with Student's t-test or Mann-Whitney test. Categorical variables were compared by Chi-square

test or Fisher's exact test. Standardized mean differences (SMDs) and p values were calculated to evaluate the differences between groups.

LCA was employed to derive phenotypes. Based on previous researches and potential association with outcomes [9, 15], we selected baseline variables reflecting the severity of the patient's disease and organ function impairment. Clinical outcomes were not included. We used Mplus (version 8.3) to fit models with latent classes. The optimal number of classes was determined by a combination of Bayesian information criterion (BIC), Entropy and the Vuong-Lo-Mendell-Rubin (VLMR) test [16].

The daily fluid balance, mean arterial pressure, need for vasopressors, PaO₂/FiO₂ which would influence decision of diuretics treatment and correlate with outcomes, were defined as time-dependent variables. The marginal structural model uses inverse probability of treatment-weighting (IPTW) estimator to create a pseudo-population, allowing the correction of time-fixed baselines and time-varying confounders [17, 18]. MSM evaluated the effect of diuretics on 28-day mortality. Several specified subgroup analyses were performed. We used RStudio (version 1.3.1073) to perform the statistical analysis. A p value of less than 0.05 was considered to be of statistical significance.

Results

Demographic and clinical characteristics

A total of 932 patients were included and 558 (59.9%) patients received diuretics within the first 48 hours since enrollment. The demographic and clinical characteristics of patients between groups were presented in Table 1. In general, patients in diuretics group had less severe disease, higher mean arterial pressure and lower proportion of vasoactive agents use than those in non-diuretics group. The all-cause 28-day mortality was significantly lower in diuretics group (84 (15.1%) vs. 105 (28.1%), p < 0.001) and the survival advantage persisted at day 90. Detailed comparisons between groups were presented in Table S2.

Table 1

Demographic and clinical characteristics of patients between groups. Values are mean (SD), median (IQR[range]), or number (proportion).

	No diuretics	Diuretics	p	SMD
N	374	558		
Age, years	50.20 (17.20)	49.58 (15.09)	0.561	0.038
Female (n,%)	172 (46.0)	261 (46.8)	0.866	0.016
Body mass index	28.93 (7.51)	28.77 (6.54)	0.801	0.023
APACHE III	97.81 (30.41)	88.20 (28.90)	< 0.001	0.324
SOFA	8.57 (2.92)	7.35 (2.38)	< 0.001	0.455
Primary lung injury (n, %)			< 0.001	0.354
Sepsis	109 (29.1)	97 (17.4)		
Trauma	28 (7.5)	45 (8.1)		
Aspiration	52 (13.9)	94 (16.8)		
Pneumonia	171 (45.7)	267 (47.8)		
Other	14 (3.7)	55 (9.9)		
Comorbidity(n, %)				
Immune suppression	27 (7.2)	44 (7.9)	0.803	0.025
Diabetes	62 (16.6)	93 (16.7)	1.000	0.002
Hypertension	82 (21.9)	139 (24.9)	0.331	0.071
Prior myocardial infarction	11 (2.9)	23 (4.1)	0.445	0.064
Congestive heart failure	10 (2.7)	17 (3.0)	0.894	0.022
Chronic pulmonary disease	32 (8.6)	29 (5.2)	0.058	0.133
Charlson Comorbidity Index	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.077	0.167
Heart rate, bpm	97.65 (19.95)	97.11 (19.41)	0.686	0.027
Respiratory rate, bpm	28.52 (7.17)	27.39 (7.51)	0.023	0.154
CVP, mmHg	11.53 (4.81)	11.71 (5.05)	0.601	0.036

Data are presented as mean (SD), median (IQR[range]), or number (proportion). APACHE III: Acute Physiology and Chronic Health Evaluation III; SOFA: sequential organ failure assessment; CVP: central venous pressure; MAP: mean arterial pressure; PaO₂/FiO₂: ratio of partial pressure of oxygen to the fractional concentration of inspired oxygen; VFDs: ventilation free days.

	No diuretics	Diuretics	p	SMD
MAP, mmHg	74.89 (13.39)	80.32 (13.54)	< 0.001	0.404
Vasopressors(n,%)	172 (46.0)	100 (17.9)	< 0.001	0.631
Fluid balance, ml	2810.77 (3261.29)	819.08 (2802.81)	< 0.001	0.655
Hemoglobin, g/dl	9.77 (1.65)	10.00 (1.62)	0.037	0.140
Platelet, x10 ¹² /L	179.63 (121.63)	200.17 (120.25)	0.013	0.170
Creatinine, mg/dl	1.35 (0.99)	1.25 (1.01)	0.151	0.098
PaO ₂ /FiO ₂ , mmHg	145.56 (72.57)	149.14 (60.19)	0.441	0.054
Clinical outcomes				
28-day mortality(n, %)	105 (28.1)	84 (15.1)	< 0.001	0.321
VFDs by day28, day	19.00[14.00,23.00]	21.00[17.25,24.00]	< 0.001	0.315
RRT by day90(n, %)	18 (7.8)	27 (11.6)	0.215	0.130
RRT days by day90, day	15.00[9.00, 32.00]	13.50[9.00, 28.50]	0.692	0.086
Data are presented as mean (SD), median (IQR[range]), or number (proportion). APACHE III: Acute Physiology and Chronic Health Evaluation III; SOFA: sequential organ failure assessment; CVP: central venous pressure; MAP: mean arterial pressure; PaO ₂ /FiO ₂ : ratio of partial pressure of oxygen to the fractional concentration of inspired oxygen; VFDs: ventilation free days.				

Association between diuretics use and 28-day mortality

Both time-fixed variables including age, APACHE III, Charlson Comorbidity Index, and time-varying confounders (as mentioned above) were adjusted by marginal structural model. The weight distribution for IPTW used to adjust for confounding factors was shown in Figure S1. Ultimately, the MSCM analysis revealed that compared with no diuretics therapy, loop diuretics use was associated with improved 28-day mortality of ARDS patients (HR 0.78; 95%CI 0.62–0.99; p = 0.04) in the overall population (Fig. 1).

Table 2 presented the fit statistics of the generated LCA models. Three phenotypes were identified: 89 (9.5%) subjects in subtype1, which mainly suffered from pneumonia, with relatively normal renal function and lowest CVP; 635 (68.1%) subjects in subtype2, characterized by almost normal serum creatinine and relatively lower CVP; and 208 (22.3%) subjects in subtype3, who were characterized by worse renal function, higher CVP, higher proportion of complications such as diabetes, hypertension and heart disease. Comparisons between phenotypes were presented in Table 3, Table S3, and Figure S2. Interestingly, patients in subtype3 could benefit from diuretics (HR 0.64; 95%CI 0.44–0.92; p = 0.02), while the results of MSCM indicated no significant association between diuretics and 28-day mortality in subtype1 or subtype2 (Fig. 2).

Table 2
Fit statistics for latent class analysis models

	BIC	Entropy	p values	Number of patients in each phenotype			
				1	2	3	4
1	51833			932			
2	51009	0.746	0.10	604	328		
3	50069	0.988	0.0001	89	635	208	
4	49635	0.902	0.03	89	213	424	206

Table 3

Comparison of baseline and clinical characteristics between subtypes. Data are presented as mean (SD), median (IQR[range]), or number (proportion).

	subtype1	Subtype2	Subtype3	p
N	89	635	208	
Age, years	46.56 (13.22)	48.34 (16.39)	55.79 (14.23)	< 0.001
Female (n,%)	33 (37.1)	291 (45.8)	109 (52.4)	0.045
Body mass index	24.23 (6.39)	29.19 (6.91)	30.61 (8.18)	< 0.001
APACHE III	110.60 (30.04)	86.76 (28.34)	99.31 (29.53)	< 0.001
Primary lung injury (n, %)				< 0.001
Sepsis	11 (12.4)	136 (21.4)	59 (28.4)	
Trauma	1 (1.1)	68 (10.7)	4 (1.9)	
Aspiration	8 (9.0)	107 (16.9)	31 (14.9)	
Pneumonia	65 (73.0)	272 (42.8)	101 (48.6)	
Other	4 (4.5)	52 (8.2)	13 (6.2)	
Comorbidity(n, %)				
Immune suppression	14 (15.7)	30 (4.7)	27 (13.0)	< 0.001
Diabetes	12 (13.5)	0 (0.0)	143 (68.8)	< 0.001
Hypertension	11 (12.4)	108 (17.0)	102 (49.0)	< 0.001
Myocardial infarction	1 (1.1)	12 (1.9)	21 (10.1)	< 0.001
Congestive heart failure	1 (1.1)	9 (1.4)	17 (8.2)	< 0.001
Chronic pulmonary disease	5 (5.6)	34 (5.4)	22 (10.6)	0.028
Charlson Comorbidity Index	6.00 [6.00, 6.00]	0.00[0.00,0.00]	2.00 [2.00, 3.00]	< 0.001
Heart rate, bpm	99.79 (19.65)	98.13 (19.29)	93.85 (20.27)	0.011
Respiratory rate, bpm	30.20 (8.30)	27.45 (7.21)	28.03 (7.38)	0.005

	subtype1	Subtype2	Subtype3	p
CVP, mmHg	10.24 (5.91)	11.64 (4.81)	12.22 (4.85)	0.008
MAP, mmHg	74.24 (11.37)	78.95 (13.80)	77.45 (14.16)	0.008
Vasopressors(n,%)	0.27 (0.45)	0.27 (0.45)	0.36 (0.48)	0.071
Fluid balance, ml	2094.21 (2833.58)	1412.33(3181.05)	2002.85(3120.95)	0.021
Hemoglobin, g/dl	9.29 (1.55)	10.14 (1.66)	9.49 (1.44)	< 0.001
Platelet, x10 ¹² /L	185.94 (100.06)	192.06 (121.98)	194.40 (127.19)	0.862
Creatinine, mg/dl	1.16 (0.73)	1.21(0.99)	1.56 (1.08)	< 0.001
PaO ₂ /FiO ₂ , mmHg	144.68 (73.49)	147.50 (62.00)	149.69 (70.95)	0.836
Clinical outcomes				
28-day mortality(n, %)	37 (41.6)	92 (14.5)	60 (28.8)	< 0.001
VFDs by day28, day	21.00[15.25,24.00]	21.00[16.00,24.00]	20.00[16.00,24.00]	0.922
RRT by day90(n,%)	5 (5.7)	34 (5.4)	24 (11.5)	0.008
RRT days, day	31.00[15.00,34.00]	16.00[8.75,30.00]	12.00[9.00,29.50]	0.391

Subgroup analysis suggested that diuretics use was correlated with reduced 28-day mortality among patients with initial MAP equal or more than 65mmHg, PaO₂/FiO₂ equal or less than 150mmHg, and no interaction was detected. Besides, the association seemed to be stronger in female and sepsis induced ARDS patients, and the interaction was significant. Other results of the subgroup analyses were presented in Fig. 1 and Table S4.

Discussion

In the present study, we found that early loop diuretics were associated with reduced 28-day mortality in ARDS patients after adjustment of both time-fixed and time-varying confounders. LCA identified three phenotypes and patients in subtype3 who were characterized by worse renal function and higher CVP, might benefit from diuretics. Subgroup analysis indicated that the association between diuretics and reduced 28-day mortality was more remarkable among female, sepsis induced ARDS, and those with lower PaO₂/FiO₂ (< = 150mmHg), higher MAP (> = 65mmHg).

Fluid therapy is the fundamental treatment for ARDS, while volume overload is rather common and related to increased risk of death^[19]. Diuretics are frequently prescribed in the critically ill to facilitate

liquid removal and have become a pharmacologic adjuvant therapy in ARDS^[20]. Studies found that compared with liberal fluid strategy or standard care, conservative fluid management achieved by restricting fluid intake, use of diuretics or hemofiltration, was associated with improved oxygenation, increased ventilation free days, and decreased mortality^[21–24]. What's more, it has been proposed that correction of fluid retention may rely on diuretics or renal replacement therapy once the hemodynamic status is stabilized^[25]. Of note, early diuretics use was independently associated with lower mortality, which had been found in a less rigorous study, using logistics regression based on the time-fixed baseline variables^[7]. We explored the effect of diuretics on 28-mortality using MSCM to adjust time-dependent confounders, and the results further support its use in ARDS patients.

There are evident distinctions in the etiology, physiology, and biology of ARDS patients, leading to different responses to the same therapy^[10]. We identified three subtypes by LCA and MSCM indicated that diuretics correlated with reduced 28-day mortality in subtype3, who were distinguished by elevated serum creatinine, higher CVP, more complications including diabetes mellitus, hypertension and heart disease. Previous study has found that in ARDS patients especially with concomitant acute kidney injury, positive fluid balance was associated with higher mortality^[26]. However, when used appropriately, frusemide may prevent and even resolve acute kidney injury as well as improving survival^[27, 28]. Further research revealed that diuretics were significantly associated with lower mortality in the positive fluid balance subgroup while insignificant in the negative fluid balance subgroup^[29]. Moreover, diuretics have been recommended in patients with hypertension and heart failure to promote water and sodium excretion and reduce volume load^[30, 31]. The effect of diuretics on mortality might be attributed to the improvement of renal function and reduction of fluid retention.

Fluid resuscitation is highly recommended in sepsis management^[32] while persistent positive fluid balance was an independent risk factor for death^[33]. Actually, in ARDS patients complicated by septic shock, achieving both early goal-directed cardiovascular resuscitation and late conservative fluid therapy was related to the lowest mortality^[34]. So far, the conservative strategy has been recommended for sepsis-induced ARDS who do not have evidence of tissue hypoperfusion^[32]. The results that the diuretics correlated with decreased mortality in sepsis-induced ARDS patients and those with higher MAP are consistent with the current clinical practice. Additionally, we found that diuretics might be favorable to patients with $\text{PaO}_2/\text{FiO}_2 \leq 150\text{mmHg}$, possibly due to the reduction of EVLW. Since EVLW estimates the fluid in pulmonary interstitial and alveolar spaces, and is strongly associated with deterioration of $\text{PaO}_2/\text{FiO}_2$, severer lung injury and higher mortality^[3, 35], and decrease in EVLW may be associated with improved survival^[36]. We postulated that diuretics may obviously alleviate pulmonary edema in the worse oxygenation subgroup and contribute to better survival.

The present study is the first to explore the effect of loop diuretics use on 28-day mortality of ARDS patients, using MSCM to account for both time-fixed and time-dependent confounders. The phenotypes derived based on variables accessible from medical history and routine laboratory tests may inspire

clinicians to more precise treatment. Also we have to acknowledge that several limitations exist. Firstly, we were unable to adjust confounders after the first seven days, since the original trial was planned for a maximum of one week. However, when evaluating seven-day mortality, the benefit of diuretics was also significant (Table S5). The survival advantage of diuretics treatment might persist for a long time. Secondly, we did not include inflammatory biomarkers in LCA, due to limited access to data extraction. Nevertheless, we divided the patients into three categories of mild, moderate and severe disease severity, which was in accordance with clinical practice. In addition, the retrospective secondary analysis was insufficient to explain the causality, well designed randomized controlled clinical trials are required.

Conclusion

Loop diuretics use was associated with reduced 28-day mortality of ARDS patients, after correction of time-dependent variables. This association was even significant in female, sepsis induced ARDS and moderately ill patients. Future randomized controlled trials are required to validate these results.

List Of Abbreviations

HR: hazard ratio; CI: confidence of interval; APACHE III: Acute Physiology and Chronic Health Evaluation III; SOFA: sequential organ failure assessment; CVP: central venous pressure; MAP: mean arterial pressure; PEEP: positive end expiration pressure; Pplat: plateau pressure; LOS: length of stay; ICU: intensive care unit; VFDs: ventilation free days; MSCM: Marginal structural Cox model; LCA: Latent class model.

Declarations

Ethics approval and consent to participate

This was a secondary analysis of a prospective RCT which was approved by the institutional review board at each study center, and informed consent was obtained from the patients or their surrogates. All the information was de-identified in the downloaded dataset. The ethical approval statement and the need for informed consent were waived for this manuscript.

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Authors' contributions

RZ and HC contributed equally to this work. RZ carried out the design, participated in the collection and assembly of data and drafted the manuscript. HC wrote part of the manuscript. HC, ZWG, MHL, YY, HBQ

participated in the manuscript revision. LL carried out the design, manuscript writing and final approval of this research. All authors read and approved the final version before submission.

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Availability of data and materials

The datasets presented in the current study are available in the BioLINCC website. (<https://biolincc.nhlbi.nih.gov>)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

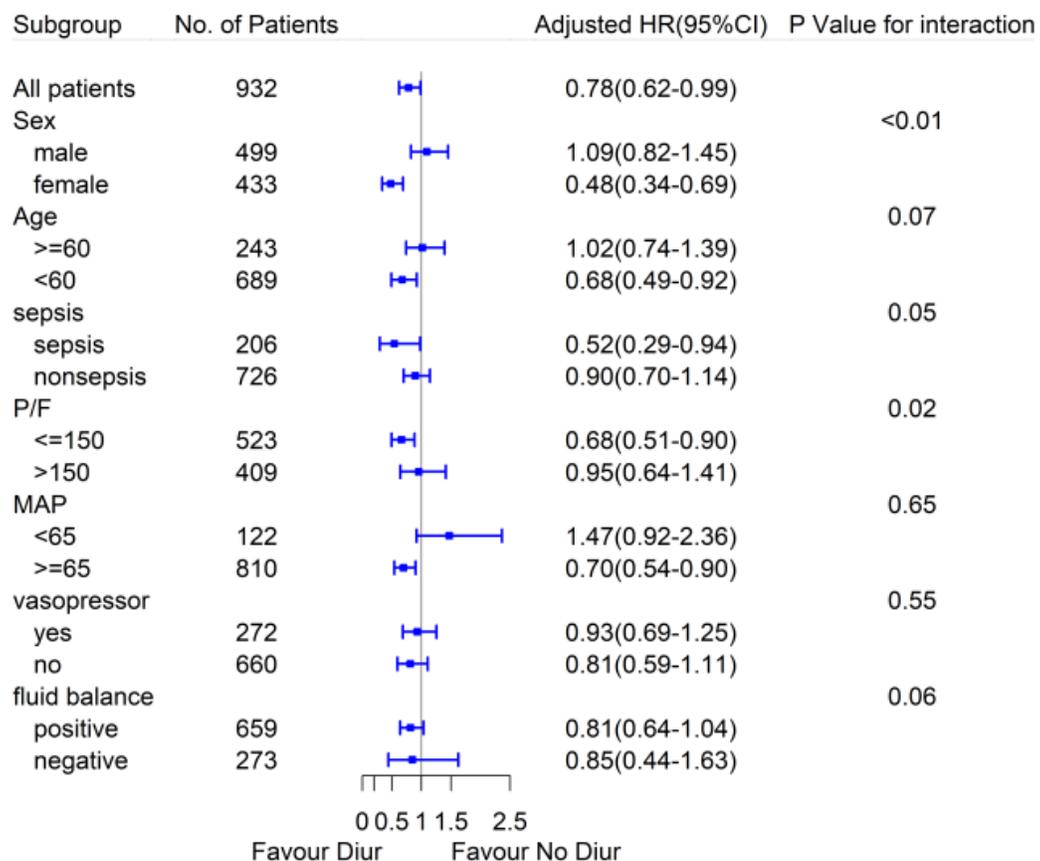


Figure 1

Marginal structural Cox model hazard ratio values for 28-day mortality in diuretics and no diuretics group according to the subgroups.

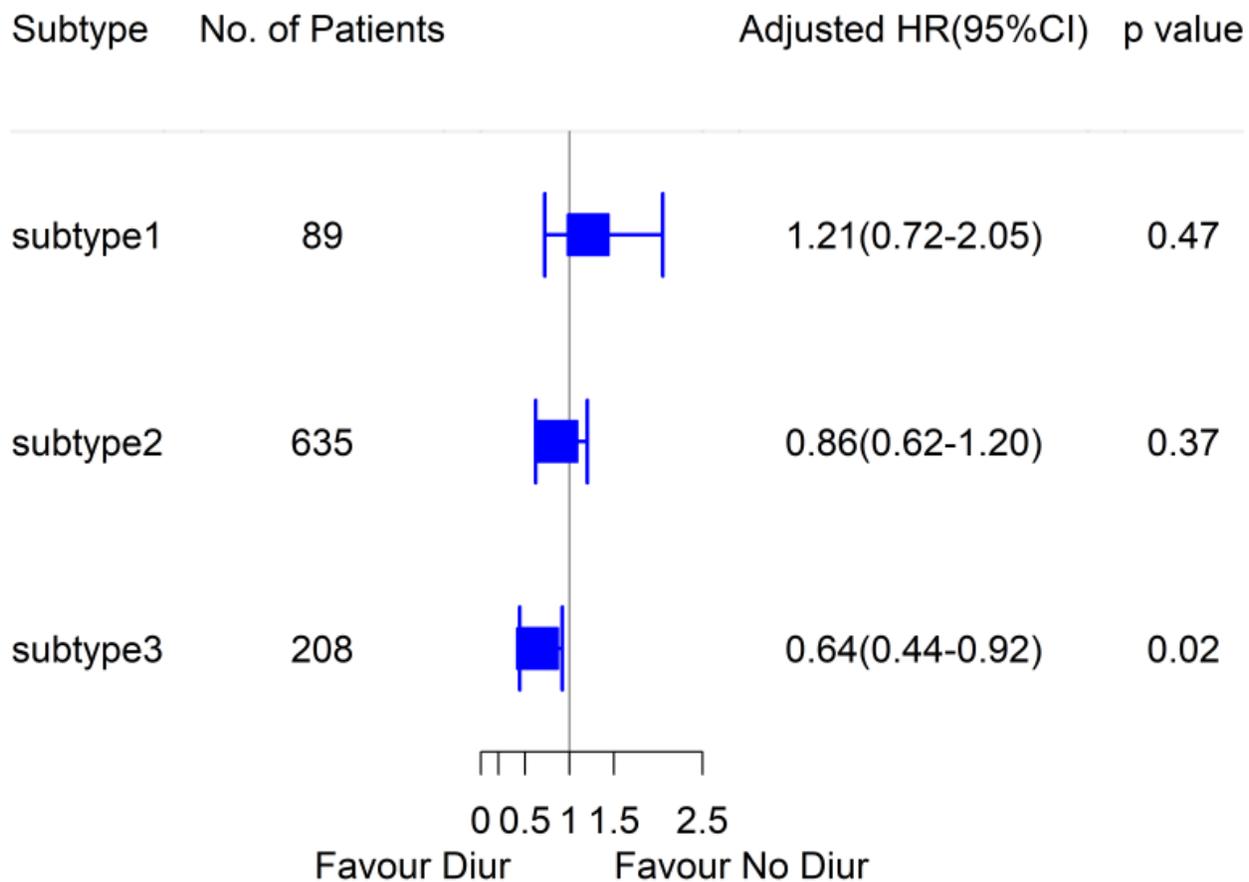


Figure 2

Marginal structural Cox model hazard ratio values for 28-day mortality in diuretics and no diuretics group according to the subtypes derived by LCA.

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