

# Exploratory Non-Causal Associations of Variables with New-Onset Atrial Fibrillation Incidence and Mortality in Critically Ill Patients [Response To Letter]

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## Dear editor

We express our gratitude to Dr. Yanyan Song for their thoughtful letter concerning our article, "Impact of New-Onset Atrial Fibrillation on Mortality in Critically Ill Patients", published in *Clinical Epidemiology*.<sup>1</sup> We appreciate the opportunity to address the valuable points raised, which provide important considerations for interpreting our findings and shaping future research.

Dr. Song highlights the potential influence of surgery type on the incidence of new-onset atrial fibrillation (AF) and its association with mortality. We acknowledge that the incidence of new-onset AF is higher after cardiac surgery compared to non-cardiac surgery, as noted in prior studies. To address this, we are now providing additional data using the Medical Information Mart for Intensive Care (MIMIC)-IV database, including surgery type and heart failure (HF) type distributions by atrial fibrillation status (Table 1), with 22.54% of new-onset AF patients having undergone heart surgery, 63.89% non-heart surgery, and 13.57% no surgery, compared to 10.36%, 70.64%, and 18.99% in the no-AF group, respectively ( $p < 0.001$ ). As new-onset AF was diagnosed at discharge and could occur anytime during hospitalization, not necessarily post-surgery, we provide further analysis of post-surgery new-onset AF incidence by surgery type in Table 2, which shows that 37.42% of patients with heart surgery and 20.20% with non-heart surgery developed AF post-surgery ( $p < 0.001$ ). To assess the impact of surgery type on mortality in new-onset AF patients, we provide mortality analysis in Table 3, which shows significantly lower 1-year mortality

**Table 1** Surgery Type and Heart Failure Type Distributions by Atrial Fibrillation Status

	Overall (n = 48018)	No AF (n = 31562)	Pre-Existing AF (n = 4877)	New-Onset AF (n = 11579)	P value*
Surgery type					< 0.001
No surgery	8423 (17.54%)	5995 (18.99%)	857 (17.57%)	1571 (13.57%)	
Heart surgery	6593 (13.73%)	3271 (10.36%)	712 (14.60%)	2610 (22.54%)	
Non-heart surgery	33002 (68.73%)	22296 (70.64%)	3308 (67.83%)	7398 (63.89%)	
HF type					< 0.001
No HF	35348 (73.61%)	26387 (83.60%)	2269 (46.52%)	6692 (57.79%)	
Systolic HF	6696 (13.94%)	2879 (9.12%)	1273 (26.10%)	2544 (21.97%)	
Diastolic HF	5200 (10.83%)	1969 (6.24%)	1211 (24.83%)	2020 (17.45%)	
Unspecified HF	774 (1.61%)	327 (1.04%)	124 (2.54%)	323 (2.79%)	

**Note:** \*Comparisons among three subgroups.

**Abbreviations:** AF, atrial fibrillation; HF, heart failure.

**Table 2** Post-Surgery New-Onset Atrial Fibrillation Incidence and Mortality by Surgery Type

	<b>Overall (n = 48018)</b>	<b>No Surgery (n = 8423)</b>	<b>Heart Surgery (n = 6593)</b>	<b>Non-Heart Surgery (n = 33002)</b>	<b>P value*</b>
New-onset AF type					< 0.001
No new-onset AF	36439 (75.89%)	6852 (81.35%)	3983 (60.41%)	25604 (77.58%)	
New-onset AF after surgery	9134 (19.02%)	0 (0.00%)	2467 (37.42%)	6667 (20.20%)	
New-onset AF not related to surgery	2445 (5.09%)	1571 (18.65%)	143 (2.17%)	731 (2.22%)	
Mortality					
ICU mortality	3246 (6.76%)	279 (3.31%)	201 (3.05%)	2766 (8.38%)	< 0.001
In-Hospital mortality	4689 (9.77%)	455 (5.40%)	295 (4.47%)	3939 (11.94%)	< 0.001
3-month mortality	8378 (17.45%)	1207 (14.33%)	478 (7.25%)	6693 (20.28%)	< 0.001
6-month mortality	9930 (20.68%)	1489 (17.68%)	589 (8.93%)	7852 (23.79%)	< 0.001
1-year mortality	11862 (24.70%)	1869 (22.19%)	728 (11.04%)	9265 (28.07%)	< 0.001

**Note:** \*Comparisons among three subgroups.

**Abbreviations:** AF, atrial fibrillation; HF, heart failure; ICU, intensive care unit.

**Table 3** Mortality by Surgery Type in Post-Surgery New-Onset Atrial Fibrillation

	<b>New-Onset AF After Heart Surgery (n = 2467)</b>	<b>New-Onset AF After Non-Heart Surgery (n = 6667)</b>	<b>P value*</b>
Mortality			
ICU mortality	74 (3.00%)	947 (14.20%)	<0.001
In-Hospital mortality	115 (4.66%)	1336 (20.04%)	<0.001
3-month mortality	188 (7.62%)	2070 (31.05%)	<0.001
6-month mortality	231 (9.36%)	2372 (35.58%)	<0.001
1-year mortality	287 (11.63%)	2717 (40.75%)	<0.001

**Note:** \*Comparisons between two groups.

**Abbreviation:** AF, atrial fibrillation; ICU, intensive care unit.

for post-surgery new-onset AF after heart surgery (11.63%) compared to non-heart surgery (40.75%) ( $p < 0.001$ ). [Table 2](#) data further indicate consistently lower mortality rates across time points for heart surgery patients compared to non-heart surgery patients (see [Table 2](#) for details). This suggests that new-onset AF, particularly post-surgery, in non-cardiac surgery patients is associated with worse outcomes, possibly due to a broader range of underlying conditions, less specialized cardiac monitoring, or differences in perioperative management compared to cardiac surgery patients, who benefit from targeted protocols. We agree that further studies stratifying mortality outcomes by surgery type and AF onset timing could provide deeper insights into these differences and the underlying mechanisms driving them.

Second, Dr. Song notes the lack of analysis on the influence of pressor or inotropic agents on new-onset AF. Our original article reported higher use of inotropes and vasopressors in the new-onset AF group (54.64%) compared to the no-AF (32.60%) and pre-existing AF (42.55%) groups ( $p < 0.001$ ), suggesting a potential association. However, evaluating the specific role of these medications in triggering AF was not within our study's scope. We appreciate this suggestion and encourage future research to use advanced statistical methods, such as mediation analysis, to explore this relationship.

Third, Dr. Song suggests examining AF incidence and mortality outcomes based on heart failure (HF) types and cardiac function, particularly using N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. To address this, we are now providing data of new-onset AF incidence by HF type ([Table 1](#)), showing that among patients with no HF ( $n=35,348$ ), 18.93% developed new-onset AF; among systolic HF patients ( $n=6696$ ), 38.00%; among diastolic HF patients ( $n=5200$ ), 38.85%; and among unspecified HF patients ( $n=774$ ), 41.73% ( $p < 0.001$ ). These results indicate a significantly higher incidence of new-onset AF in patients with HF, particularly those with unspecified HF, compared to those without HF. We also provide new-onset atrial fibrillation incidence and mortality by heart failure type in [Table 4](#), which shows that new-onset AF after surgery was more frequent in patients with unspecified HF (29.84%) compared to those with no HF (15.27%) ( $p < 0.001$ ). Mortality was higher across all HF types, with unspecified HF patients exhibiting the highest 1-year mortality (46.51%) compared to no HF (21.40%),

**Table 4** New-Onset Atrial Fibrillation Incidence and Mortality by Heart Failure Type

	No HF (n = 35348)	Systolic HF (n = 6696)	Diastolic HF (n = 5200)	Unspecified HF (n = 774)	P value*
New-onset AF type					< 0.001
No new-onset AF	28656 (81.07%)	4152 (62.01%)	3180 (61.15%)	451 (58.27%)	
New-onset AF after surgery	5396 (15.27%)	2035 (30.39%)	1472 (28.31%)	231 (29.84%)	
New-onset AF not related to surgery	1296 (3.67%)	509 (7.60%)	548 (10.54%)	92 (11.89%)	
Mortality					
ICU mortality	2142 (6.06%)	593 (8.86%)	368 (7.08%)	143 (18.48%)	< 0.001
In-Hospital mortality	3063 (8.67%)	837 (12.50%)	581 (11.17%)	208 (26.87%)	< 0.001
3-month mortality	5367 (15.18%)	1550 (23.15%)	1176 (22.62%)	285 (36.82%)	< 0.001
6-month mortality	6367 (18.01%)	1824 (27.24%)	1425 (27.40%)	314 (40.57%)	< 0.001
1-year mortality	7566 (21.40%)	2167 (32.36%)	1769 (34.02%)	360 (46.51%)	< 0.001

**Note:** \*Comparisons among three subgroups.

**Abbreviations:** AF, atrial fibrillation; HF, heart failure; ICU, intensive care unit.

with systolic and diastolic HF showing intermediate rates (see Table 4 for details). These findings suggest that new-onset AF post-surgery in patients with HF, particularly unspecified HF, is associated with significantly worse outcomes, possibly due to underlying severe cardiac dysfunction or comorbidities not captured in the HF classification. However, as our study did not directly assess causality, these results are exploratory and warrant further investigation. Moreover, we excluded NT-proBNP and other cardiac enzymes from our analysis due to limited values in the MIMIC-IV database, with NT-proBNP having over 50% missing values. We agree that NT-proBNP is a critical prognostic marker, and prospective studies with comprehensive biomarker data are needed to assess its role in new-onset AF and mortality.

Fourth, Dr. Song raises the issue of ventricular rate and duration of new-onset AF episodes, which could impact hemodynamics and mortality. We concur that ventricular rates below 80 beats per minute may have less hemodynamic impact. However, the MIMIC-IV database does not provide consistent data on ventricular rates or AF episode durations in the hospitalization and intensive care unit databases, and such data might be in an independent ECG database, which requires more advanced AI algorithms and may not capture the exact time point when the patient had the first new-onset AF episode ongoing. This is part of another ongoing project by our team. Evaluating these factors was not within our study's scope, representing a limitation of our analysis. We support future research incorporating continuous electrocardiographic monitoring to assess the prognostic significance of AF characteristics.

Fifth, Dr. Song addresses the heterogeneity of the study population and the challenge of establishing causality between new-onset AF and mortality. We mitigated this by adjusting for a wide range of confounders in our multivariate Cox regression models, including demographics, comorbidities, vital signs, laboratory parameters, and treatments. Despite these efforts, residual confounding and the retrospective design preclude definitive causal conclusions, as acknowledged in our limitations. We agree that the diverse intensive care unit population introduces complexity, and prospective, multicenter studies are essential to validate our findings and explore causal mechanisms.

We sincerely thank Dr. Song for their insightful comments, which underscore key areas for advancing our understanding of new-onset AF in critically ill patients. Our study aimed to highlight the association between new-onset AF and increased mortality, and we hope it serves as a catalyst for future research addressing surgery type, medication effects, HF subtypes, AF characteristics, and causal pathways. Such efforts will enhance risk stratification and inform targeted interventions to improve patient outcomes.

## Disclosure

The authors report no conflicts of interest in this communication.

## Reference

- Zhang HD, Ding L, Mi LJ, et al. Impact of new-onset atrial fibrillation on mortality in critically ill patients. *Clin Epidemiol.* 2024;16:811–822. doi:10.2147/CLEP.S485411

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