Am J Cardiovasc Dis 2024;14(3):188-195
www.AJCD.us /ISSN:2160-200X/AJCD0155899

Review Article

Impact of frailty index on cardiovascular outcomes and readmissions of patent foramen ovale closure procedure: a propensity matched national analysis

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Received February 13, 2024; Accepted April 24, 2024; Epub June 15, 2024; Published June 30, 2024

Abstract: Background: Transcatheter patent foramen ovale (PFO) occluder device is a procedure mostly performed to prevent secondary stroke as a result of paradoxical emboli traversing an intracardiac defect into the systemic circulation. The complications and outcomes following the procedure remain poorly studied. We aimed to investigate morbidity and mortality associated with occluder device procedures using hospital frailty index score stratification. Methods: The Nationwide Readmission Database was employed to identify patients admitted for PFO closure from 2016 to 2020. Two groups divided by index frailty score were compared to report adjusted odds ratio (aOR) for primary and secondary cardiovascular outcomes. Outcomes included in-hospital mortality, acute kidney injury, acute ischemic stroke, and post-procedure bleeding. Statistical analysis was performed using *STATA v.17.* Results: Of the 2,063 total patients who underwent the procedure, 45% possessed intermediate to high frailty scores while the other 55% had low frailty scores. The first cohort had higher odds of in-hospital mortality (aOR 6.3, 95% CI 2.05-19.5), acute kidney injury (aOR 17.6, 95% CI 9.5-32.5), and stroke (aOR 3.05, 95% CI 1.5-5.8) than the second cohort. There was no difference in the incidence of post-procedural bleeding and cardiac tamponade and 30/90/180-day readmission rates between the two cohorts. Hospitalizations in the first cohort were associated with a higher median length of stay and total cost. Conclusion: High to intermediate frailty scores may predict an increased risk of in-hospital mortality in patients undergoing PFO occluder device procedures.

Keywords: Patent foramen ovale, PFO occluder device, cryptogenic stroke, PFO, frailty

Introduction

Nearly 25% of the adult population has a patent foramen ovale (PFO), a condition by itself that has not been shown to increase the risk of ischemic stroke [1]. Conversely, a PFO is highly prevalent among cryptogenic stroke patients. Up to 40% of ischemic stroke patients without an underlying cause have a PFO, suggesting a paradoxical embolism etiology [2]. Historically, the relationship between PFO and cryptogenic stroke has been controversial. For example, the Initial results of the RESPECT trial did not reveal any statistically significant benefits of PFO closure over medical therapy, however, subsequent long-term follow-up showed a reduction in ischemic stroke in the PFO closure group (HR 0.55; 95% CI [0.31-0.999]; P=0.046) and number needed to treat (45) [3, 4]. Similarly, multiple clinical trials have reported favorable outcomes such as long and short-term stroke risk of PFO closure compared to standard antiplatelet or anticoagulation therapy [5-7].

https://doi.org/10.62347/PTMD5117

Transcatheter PFO closure has been considered the primary therapy in the prevention of PFO-related stroke [8]. Like other surgical interventions, PFO closure carries the risk of perioperative complications. The Hospital Frailty Risk Score, developed by Gilbert et al., utilizes electronic health records and various diagnostic codes to evaluate frailty. Frailty assessment has gained considerable traction in the literature, with numerous studies indicating its association with adverse outcomes [9]. The frailty score includes functional assessment and baseline comorbidities such as bleeding, cardiac tamponade, and acute kidney injury. By applying a similar hospital frailty scoring system with the use of the National Readmission Database (NRD), our study was able to assess the outcomes of high to intermediate frailty score (HIFS) in patients undergoing PFO occluder device with low frailty score (LFS) patients.

Methods

Data collection

We performed a retrospective cohort study of patients admitted with index PFO closure procedures utilizing the NRD between 2016 and 2020. We queried the database for dates between 2016 and 2020 using the International Classification of Disease, Tenth Edition, Clinical Modification (ICD-10) to identify patients who underwent the occluder device procedure. The hospital frailty score was determined by applying the ICD-10 index and the distribution of comorbidities associated with frailty, as outlined in sections A1-A3 of the study conducted by Gilbert et al. The resulting scores were categorized into high frailty score (HFS; ≥15) and low-intermediate frailty score (LIFS; <15). The ICD-10 codes utilized to establish the study cohort, frailty scores, and comorbidities are detailed in the supplementary materials (Table S1). The NRD is part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality. The NRD provides discharge data from 22 states, accounting for 51.2% of the total US resident population and 49.3% of all US hospitalizations. The national US estimates were produced by using sampling weights provided by the NRD. We identified the index PFO cases with intermediate to high frailty and low frailty scores. We calculated readmission frequency with a national sample weighted at 30 days, 90 days, and 180 days post-PFO index procedure. Duplicates were removed. This data is publicly available and does not contain any HIPPA identifiers; therefore our study was exempt from institutional review board approval from our respective institutions.

Study population

Our study included all patients admitted with PFO with HFS and PFO with LIFS with an age >18 years. We excluded patients younger than 18 years, PFO performed in December for 30-day readmissions, October through December for 90 days, and July through December for 180 days of readmissions (Figure S1).

Primary and secondary outcomes

The primary outcomes were in-hospital mortality and 30-day, 90-day, and 180-day readmissions. The secondary outcomes were stroke, post-procedural bleeding, and acute kidney injury (AKI) (Table S2).

The hospital frailty risk score

The hospital frailty risk score (HFRS) is a statistical method used by the NRD to denote frailty in patients. The frailty score can be placed on a categorical spectrum with low risk (HFRS<5), intermediate risk (HFR 5-15), and high risk (HFRS>15). It was originally developed by *Gilbert et al*. using ICD-10 codes on an older model that was then tested to predict adverse outcomes in a cohort with a mean age of 79.9 years [9]. Since then, several studies have validated the scoring system, with its primary use in cohorts with a mean age >60 years of age. In our study, we pooled intermediate-risk and high-risk cohorts to compare against the low-risk cohort, using the same score range categories as in the literature.

Statistical methods

Categorical variables were analyzed using descriptive statistics with frequencies and percentages. Continuous variables were analyzed using Mean with standard or medians with interquartile range for normally distributed and skewed data. Patient demographics, comorbidities, hospital characteristics, and in-hospital outcomes were compared between PFO patients with IHFS and LFS using the Pearson χ^2 test for categorical variables and independent sample t-test for continuous variables. To further limit confounders and effect modifiers we matched comorbidities and demographics in a multivariate regression model to calculate adjusted odds ratios (aOR) for outcomes (Table S3). A trend analysis was performed. Matching variables used for multivariate regression analysis are shown in Table S4. Healthcare metrics were assessed using mean with standard device and median with interquartile range. To assess and report accurate readmissions we dropped pre-admits in the NRD dataset. We excluded periprocedural/on-table deaths due to PFO to avoid sampling bias. The STATA survey *(svy)* command was used to report nationally weighted samples. NRD hospital cost was adjusted with the national inflation index *(www.bls.gov)*. All analyses were conducted using *STATA v.17.1 TX (StataCorp).*

Results

Demographic and baseline characteristics

A total of 2,063 hospitalizations that underwent PFO occluder device procedure between 2016 and 2020 were identified, of which 45% (n=930) had IHFS at index admission while LFS constitutes 55% (n=1133). The HIFS cohort was older as compared to LFS (76 ± 6.7 vs. 74.8 ± 6.6 years). Both groups had more female patients (52% vs. 52%). Hyperlipidemia was the most common baseline comorbidity in both groups (65% vs. 63%). Detailed baseline demographics, characteristics, and comorbidities among both cohorts are described in **Table 1** and Figures S2, S3.

In-hospital complications

Complications for patients who underwent PFO occluder devices with IHFS and LFS are outlined in **Table 1**. PFO occluder cohort with IHFS had a higher complication with in-hospital mortality (6.5% vs. 1.1%, P<0.05), acute kidney injury (AKI, 37.9% vs. 4.1%, P<0.05), and stroke (9.5% vs. 2.9%, P<0.05), than those with LFS. The rate of post-procedural bleeding (2% vs. 0.8%, P<0.05) and cardiac tamponade (0.5% vs. 1.1%) did not differ between the groups.

Crude in-hospital outcomes

Univariate analysis for the in-hospital primary and secondary outcomes is illustrated in Table S5. On univariate analysis, the PFO occluder cohort with IHFS had a higher incidence of in-hospital mortality (uOR 6.03, 95% CI 2.06-17.5), AKI (uOR 14.3, 95% CI 8.2-24.9), and stroke (uOR 3.5, 95% CI 1.8-6.6) than those with LFS. The risk of cardiac tamponade (uOR 0.4, 95% CI 0.08-2.54) and post-procedural bleeding (uOR 1.5, 95% CI 0.4-5.2) were similar between the two cohorts.

Multivariate regression outcomes

Multivariate regression analysis after adjusting confounding factors including demographics and comorbidities was done. PFO occluder cohort with HIFS had a higher risk of in-hospital mortality (aOR 6.3, 95% CI 2.05-19.5), AKI (aOR 17.6, 95% CI 9.5-32.5), and stroke (aOR 3.05, 95% CI 1.5-5.8) in comparison with those with LFS. The risk of post-procedural bleeding (aOR 1.8, 95% CI 0.3-8.9) and cardiac tamponade (aOR 0.4, 95% CI 0.4-3.2) were similar between the two groups. The detailed adjusted and unadjusted estimates and proportion of outcomes between the two groups are presented in Table S5 and **Figure 1**.

Readmission rates for 30, 90, and 180 days

Even though PFO procedures hospitalizations with HIFS had worse hospital outcomes at index admission compared to PFO patients with LFS, the readmission rates at 30, 90, and 180 days were similar between both cohorts (**Figure 2**; Table S6).

Resource utilization

For HIFS patients with PFO occluder device placement, the median length of stay (LOS) at index hospitalization was 9 days (IQR 17-5) versus 1 day (IQR 4-1) for LFS patients. The most common payer type was Medicare for both of the cohorts with the median total cost at index hospitalization being $46,788 and $26,542, respectively (Table S7).

Discussion

In this study, we assessed hospital clinical outcomes and resource utilization by comparing IHFS and LIFS among patients who underwent PFO occluder device placement at index hospitalization (**Figure 3**). Our study results revealed that an IHFS was associated with worse out-

Table 1. Baseline characteristics and comorbidities of PFO occluder device procedures with IHFS vs. LFS

Baseline characteristic	Low frailty (n)	Low frailty (%)	Intermediate-High Frailty (n)	Intermediate High. Frailty (%)	*p* value
Age (Mean ± SD)	74.8 ± 6		75.9 ± 6		0.019
Sex					
Male	539	48%	443	48%	0.99
Female	594	52%	487	52%	0.99
Year					
2016	249	20.2%	181	18.9%	
2017	257	20.9%	186	19.4%	
2018	335	27.2%	282	29.5%	
2019	388	31.5%	305	31.9%	
Rehab transfer					<0.001
No rehab transfer	1,230	100%	905	94.7%	
Rehab transfer	<11	Not reportable	50	5.2%	
State resident status					
Non-Resident	95	7.7%	86	9%	
Resident	1,135	92.2%	870	90.9%	
Transfer Status					<0.001
Not a transfer or same-day event	1,198	97.3%	730	76.3%	
Transfer of 2 discharges from different hos	26	2.1%	116	12.1%	
Same Day stay of 2 discharges from different hos	<11	Not reportable	35	3.7%	
Same Day stay of 2 discharges from same hos	<11	Not reportable	40	4.2%	
Same Day stay of 3 discharges from same/different hos	<11	Not reportable	33	4.3%	
Median Household Income					0.488
0-25th percentile	270	22.3%	246	26.1%	
26-50th percentile	274	22.5%	238	25.2%	
51-75th percentile	358	29.5%	226	23.9%	
76-100th percentile	312	25.6%	232	24.6%	
Hospital Bed Size					0.6108
Small	65	5.3%	34	3.6%	
Medium	251	20.4%	193	20.2%	
Large	913	74%	278	76.1%	
Control/Ownership of Hospital					0.606
Government, non-federal	95	7.7%	93	9.7%	
Private, non-profit	965	78.4%	730	76.3%	
Private, invest own	169	13.8%	132	13.8%	
Hospital Urban/Rural Designation					0.002
Large metropolitan	824	67%	732	76.5%	
Small metropolitan	391	31.8%	208	21.8%	
Micropolitan	14	1.1%	15	1.6%	
Teaching status of the hospital					0.589
Metropolitan non-teaching	119	9.7%	90	9.4%	
Metropolitan Teaching	1,096	89.1%	845	88.8%	
Non-metropolitan	14	1.1%	15	1.6%	
Admission Day					<0.001
Monday-Friday	1,153	93.7%	776	81.2%	
Saturday-Sunday	77	6.2%	179	18.7%	
Primary Expected Payer					0.037
Medicare	1,076	87.4%	871	91.3%	
Medicaid	<11	Not reportable	<11	Not reportable	
Private	121	9.8%	47	4.9%	
Self-pay	<11	Not reportable	<11	Not reportable	
Other	19	1.6%	14	1.5%	

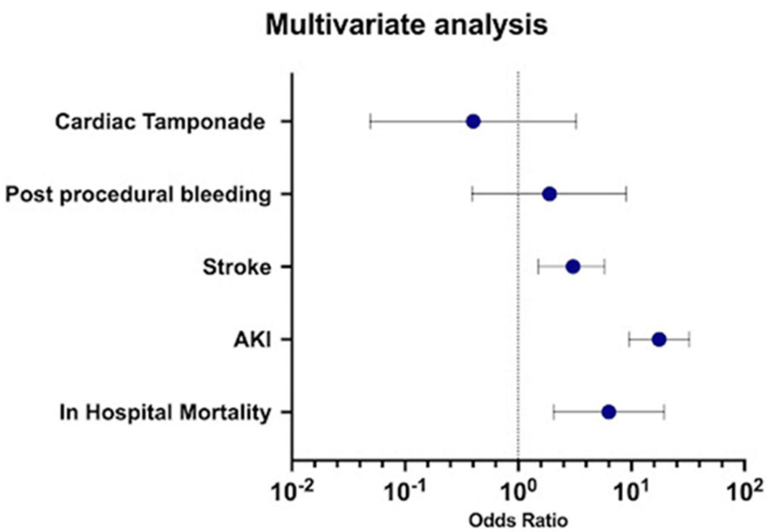

Figure 1. Forest plot depicting adjusted outcomes of PFO occluder device procedures with IHFS vs. LFS.

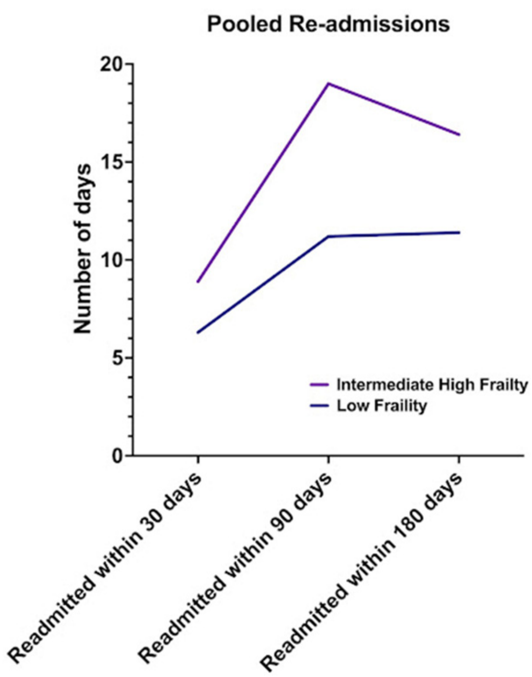

Figure 2. Pooled 30-, 90-, and 180-day readmission rates in PFO occluder device procedures with IHFS vs. LFS.

comes with a higher rate of in-hospital mortality, stroke, and AKI. The high to intermediate frailty index cohort was also found to have significantly longer hospital stays and higher utilization costs than the low frailty group among patients that underwent PFO closure. However, the rate of, post-procedural bleeding, cardiac tamponade, and readmission rates at 30, 90, and 180 days did not differ between the groups. The results mostly remained unchanged after adjustment for the potential confounding variables using multivariate logistic regression. We found that the high to intermediate frailty group was older with a higher prevalence of comorbidities including hyperlipidemia, hypertension, and obesity.

A frailty index for stratification of outcomes in patients with PFO closure is rarely used, and data on high frailty risk score patients have not been investigated. No studies on PFO closures have used a cohort that was defined to have a high fragility index stratification. To our knowledge, our analyses with the NRD are the first to provide outcomes on individuals with high frailty who underwent a PFO closure procedure.

PFO closure has been validated as a preventative measure against complication reoccurrence, despite rates of device failure in both prospective randomized controlled trials and subsequent systemic review [5, 10, 11]. Yet in these studies, individuals with multiple comorbidities, including uncontrolled diabetes mellitus, uncontrolled hypertension, a recent history of drug and alcohol abuse, and autoimmune disease were excluded [5]. Published reports that included cohorts with multiple comorbidities that underwent transcatheter PFO closure found that increasing age (>60 years of age) and multiple medical comorbidities were risk factors for morbidity, mortality, and reoccurrence of PFO complications including stroke after device implementation [12, 13]. Consequently, our high-risk cohort had an average age of 57.9 years of age, with more complications, corroborating that increased age combined with a higher HFRS may predict worse outcomes from PFO closure. Our analysis was in line with the literature that a higher mortality rate in IHFS, advanced age, and higher prevalence of comorbidities can explain worse outcomes in the IHFS group compared to LFS. Other studies have indicated similar results that the presence of atherosclerotic risk fac-

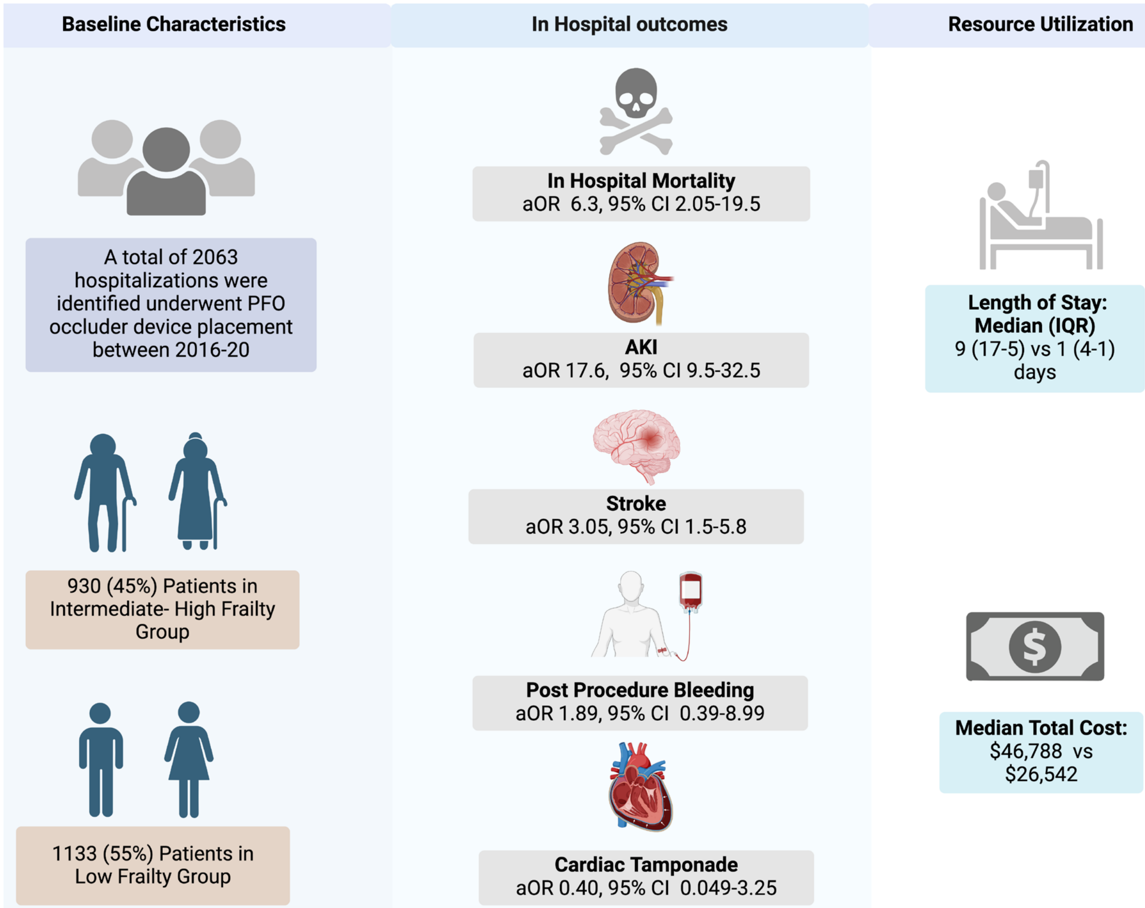

Figure 3. Graphical illustration of clinical outcomes in PFO occluder device procedures with IHFS vs. LFS.

tors, including diabetes, hypertension, and hyperlipidemia, have been found to increase the reoccurrence of complications after PFO closure [14]. A higher HFRS is influenced by increasing age and the presence of multiple comorbidities, which was evident within our high-risk cohort characteristics. Due to the large disparity in outcomes, this might indicate that patients with HFRS may not benefit from a PFO closure, as the risk of adverse outcomes becomes far greater when compared to the low-risk group. Furthermore, the use of HFRS in stratifying PFO closure may serve as an important clinical tool to predict patient prognosis, but the validation of these methods has yet to be reported.

Multiple recent meta-analyses also showed the benefit of PFO closure in reducing the recurrence of strokes however with a higher percent of patients developing post-procedural atrial fibrillation/flutter, as compared to medical therapy [11, 13, 15-17]. This data may explain the higher stroke rate in our IHFS cohort when combined with multiple atherosclerotic risk factors and advanced age.

The HFRS was originally developed with a cohort of individuals aged >75 years of age and was subsequently validated in the same study on a cohort with an average age of 79.9 years of age. This may skew the utility of predictability towards older patients, compared to the average age of patients in our low-risk and high to intermediate-risk cohorts. These findings though must be considered against the limitations of the data source. The NRD is a national representative database therefore certain demographics (location, race, ethnicity), the severity of illness during each readmission, and influential details from the patient's hospital course at each recorded readmission were not available for analysis. These factors may relate to the outcomes we have reported here and may limit generalizability within these circumstances. Furthermore, the database does not link each hospitalization together with multiple readmissions of the same patient. This limitation may skew the cohort used in our study and may influence our recorded outcomes, especially since patients undergoing PFO closure have been reported by literature to have subsequent complications that require readmissions. Finally, there is no ability for a multi-year cohort of patients to be observed due to the lack of hospitalization linking. The database instead provides data yearly, which can then be pooled together. This process was performed as part of our study's methodology to provide a surrogate for a longitudinal cohort by accumulating 4 years of the total data during our study window.

Limitations

Our study has several limitations that must be taken into consideration while interpreting results. First, NRD is an administrative dataset and relies on accurate coding, which can be subject to errors in entry. There is a potential for overlap in the indications of both patent foramen ovale (PFO) occluder devices and atrial septal defect (ASD) occluder devices. Unfortunately, the database did not include the Risk of Paradoxical Embolism (ROPE) score. Additionally, details such as the shunt's size and flow direction (left to right or right to left) based on pressure hemodynamics were absent from the database. The typical requirement of a rim greater than 5 mm for an appropriate fit of the PFO occluder device was also not covered by the database. Furthermore, information regarding distinctions between transcatheter devices utilized in PFO occluder procedures was unavailable, as differences might exist due to variations among manufacturers.

Second, the frailty score calculation in this study was based on ICD-10 codes, which primarily reflect events occurring during hospitalization. This may limit the accuracy and generalizability of the frailty score as a predictor of outcomes, as it does not consider pre-hospitalization or long-term factors that contribute to frailty. Additionally, the frailty score used can only be computed after a patient is discharged, therefore limiting its utility as a real-time risk stratification tool at the time of presentation. This constraint diminishes its practical application for informing decisions about the risks versus benefits of specific interventions, such as PFO closure, based on frailty status. Third, some of the inclusion variables in the frailty score are also part of major in-hospital outcomes such as AKI, which can lead to inflated associations between frailty scores and major adverse events. This overlap makes it difficult to separate the effects of frailty from the effects of these shared variables, potentially confounding the interpretation of the results. Finally, despite the extensive adjustment for confounders in our analysis, there is a chance of observational biases and unmeasured variables as with all retrospective studies. The temporal sequence of the events and the causal relationship cannot be determined using the HCUP databases. Given the nature of the dataset used, long-term follow-up of the PFO closure procedure was not available, and all outcomes were *in-hospital* outcomes therefore our results may not be generalizable.

Conclusion

The hospital frailty index score can be a valuable tool for periprocedural risk assessment to predict cardiovascular outcomes. In patients that undergo PFO occluder device procedure, regardless of age, frailty index score can be helpful as baseline higher comorbidities with HFS>15 can suggest worse cardiovascular outcomes with a higher length of stay and hospital cost.

Disclosure of conflict of interest

None.

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References

[1] Singh K, Neil CJ, Nguyen TH, Stansborough J, Chong CR, Dawson D, Frenneaux MP and Horowitz JD. Dissociation of early shock in takotsubo cardiomyopathy from either right or left ventricular systolic dysfunction. Heart Lung Circ 2014; 23: 1141-1148.

[2] Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D and Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988; 318: 1148-1152.

[3] Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS and Tirschwell DL; RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013; 368: 1092-1100.

[4] Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS and Tirschwell DL; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017; 377: 1022-1032.

[5] Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, Spence JD and Thomassen L; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017; 377: 1033-1042.

[6] Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Béjot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour JC, Zuber M, Favrole P, Pinel JF, Apoil M, Reiner P, Lefebvre C, Guérin P, Piot C, Rossi R, Dubois-Randé JL, Eicher JC, Meneveau N, Lusson JR, Bertrand B, Schleich JM, Godart F, Thambo JB, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C, Moulin T, Juliard JM and Chatellier G; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med 2017; 377: 1011-1021.

[7] Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, Song JM, Kang DH, Kwon SU, Kang DW, Lee D, Kwon HS, Yun SC, Sun BJ, Park JH, Lee JH, Jeong HS, Song HJ, Kim J and Park SJ. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. J Am Coll Cardiol 2018; 71: 2335-2342.

[8] Lanctôt KL, Lindsay MP, Smith EE, Sahlas DJ, Foley N, Gubitz G, Austin M, Ball K, Bhogal S, Blake T, Herrmann N, Hogan D, Khan A, Longman S, King A, Leonard C, Shoniker T, Taylor T, Teed M, de Jong A, Mountain A, Casaubon LK, Dowlatshahi D and Swartz RH; Management of Mood, Cognition and Fatigue Following Stroke Best Practice Writing Group, the Heart & Stroke Canadian Stroke Best Practices and Quality Advisory Committee; in collaboration with the Canadian Stroke Consortium. Canadian stroke best practice recommendations: mood, cognition and fatigue following stroke, 6th edition update 2019. Int J Stroke 2020; 15: 668-688.

[9] Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, Arora S, Street A, Parker S, Roberts HC, Bardsley M and Conroy S. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet 2018; 391: 1775-1782.

[10] Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, Spence JD and Søndergaard L; Gore REDUCE Clinical Study Investigators. Five-year outcomes of PFO closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2021; 384: 970-971.

[11] Turc G, Calvet D, Guérin P, Sroussi M, Chatellier G and Mas JL; CLOSE Investigators. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. J Am Heart Assoc 2018; 7: e008356.

[12] Merkler AE, Gialdini G, Yaghi S, Okin PM, Iadecola C, Navi BB and Kamel H. Safety outcomes after percutaneous transcatheter closure of patent foramen ovale. Stroke 2017; 48: 3073-3077.

[13] Ahmad Y, Howard JP, Arnold A, Shin MS, Cook C, Petraco R, Demir O, Williams L, Iglesias JF, Sutaria N, Malik I, Davies J, Mayet J, Francis D and Sen S. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. Eur Heart J 2018; 39: 1638-1649.

[14] Wallenborn J, Bertog SC, Franke J, Steinberg DH, Majunke N, Wilson N, Wunderlich N and Sievert H. Recurrent events after percutaneous closure of patent foramen ovale. Catheter Cardiovasc Interv 2013; 82: 541-546.

[15] Nasir UB, Qureshi WT, Jogu H, Wolfe E, Dutta A, Majeed CN and Tan WA. Updated meta-analysis of closure of patent foramen ovale versus medical therapy after cryptogenic stroke. Cardiovasc Revasc Med 2019; 20: 187-193.

[16] Shah R, Nayyar M, Jovin IS, Rashid A, Bondy BR, Fan TM, Flaherty MP and Rao SV. Device closure versus medical therapy alone for patent foramen ovale in patients with cryptogenic stroke: a systematic review and meta-analysis. Ann Intern Med 2018; 168: 335-342.

[17] Ntaios G, Papavasileiou V, Sagris D, Makaritsis K, Vemmos K, Steiner T and Michel P. Closure of patent foramen ovale versus medical therapy in patients with cryptogenic stroke or transient ischemic attack: updated systematic review and meta-analysis. Stroke 2018; 49: 412-418.

Table S1. ICD 10 codes for cohort identification and stratification with major baseline comorbidities

Variable	ICD-10 CM Codes
Outcomes	
PFO closure procedure	02U53JZ
Acute Kidney Injury	N171, N172, N178, N179, N19, N170
Cardiac Shock	R570
Mechanical Circulatory Support	5A02110, 5A02210, 5A0211D, 02HA3RZ, 5A02116, 5A0221D, 5A1522F, 5A1522G, 5A1522H, 5A15A2F, 5A15A2G, 5A15A2H, 5A15223
Myocardial Infarction	I121, I121.0, I21.1, I21.2, I21.3, I21.4, I21.5, I21.6, I21.7, I21.8, I21.9, I22, I22.1, I22.2, I22.3, I22.4, I22.5, I22.6, I22.7, I22.8, I22.9
Stroke	I639, 638, I6359, I63549, I63219, I63212, I63211, I6320, I6309, I63039, I63032, I63031, 6302, I63019, 63012, 63011, I6300
Hospital Frailty Score ICD 10 code for frailty calculation	"F00" "F02**" "F04**" "G81**" "G30**" "I69**" "R29**" "N39**" "F05**" "W19**" "S00**" "R31**" "B96**""R41**" "R26**" "I67**" "R56**" "R40**" "T83**" "S06**" "S42**" "E87**" "M25**" "E86**" "R54**" "Z50**" "F03**" "W18**" "Z75**" "F01**" "S80**" "L03**" "H54**" "E53**" "Z60**" "G20**" "R55**" "S22**" "K59**" "N17**" "L89**" "Z22**" "B95**" "L97**" "R44**" "K26**" "I95**" "N19**" "A41**" "Z87**" "J96**" "X59**" "M19**" "G40**" "M81**" "S72**" "S32**" "E16**" "R94**" "N18**" "R33**" "R69**" "N28**" "R32**" "G31**" "Y95**" "S09**" "R45**" "G45**" "Z74**" "M79**" "W06**" "S01**" "A04**" "A09**" "J18**" "J69**" "R47**" "E55**" "Z93**" "R02**" "R63**" "H91**" "W10**" "W01**" "E05**" "M41**" "R13**" "Z99**" "U80**" "M80**" "K92**" "I63**" "N20**" "F10**" "Y84**" "R00**" "J22**" "Z73**" "R79**" "Z91**" "S51**" "F32**" "M48**" "E83**" "M15**" "D64**" "L08**" "R11**" "K52**" "R50**"
Comorbidities*	
PAD	I730, I7300, I7301, I731, I738, I7389, I739
Family hx of CAD	Z8249, Z8241
OSA	G4733
Liver disease	K700, K701, K7010, K7011, K702, K703, K7030, K7031, K704, K7040, K7041, K709, Q898, Q446, I820, R160, K7460, K710, K711, K7110, K7111, K712, K713, K714, K715, K7150, K7151, K716, K717, K718, K719, K760, K761, K762, K763, K764, K765, K766, K767, K768, K7681, K7689, K769
Illicit Drugs	F191, F1910, F1911, F1912, F19120, F19121, F19122, F19129, F1914, F1915, F19150, F19151, F19159, F1916, F1917, F1918, F19180, F19181, F19182, F19188, F1919, F192, F1920, F1921, F1922, F19220, F19221, F19222, F19229, F19230, F19231, F19232, F19239, F1924, F1925, F19250, F19251, F19259, F1926, F1927, F1928, F19280, F19281, F19282, F19288, F1929, F199, F1990, F1992, F19920, F19921, F19922, F19929, F1993, F19930, F19931, F19932, F19939, F1994, F1995, F19950, F19951, F19959, F1996, F1997, F1998, F19980, F19981, F19982, F19988, F1999
Alcohol	F101, F1010, F1011, F1012, F10120, F10121, F10129, F1014, F1015, F10150, F10151, F10159, F1018, F10180, F10181, F10182, F10188, F1019, F102, F1020, F1021, F1022, F10220, F10221, F10229, F1023, F10230, F10231, F10232, F10239, F1024, F1025, F10250, F10251, F10259, F1026, F1027, F1028, F10280, F10281, F10282, F10288, F1029, F10920, F10921, F10929, F1094, F1095, F10950, F10951, F10959, F1096, F1097, F1098, F10980, F10981, F10982, F10988, F1099
Smoking	F17, F172, F1720, F17200, F17201, F17203, F17208, F17209, F1721, F17210, F17211, F17213, F17218, F17219, F1722, F17220, F17221, F17223, F17228, F17229, F1729, F17290, F17291, F17293, F17298, F17299, Z87891

Prior PCI	Z986, Z9861, Z9862
Prior CABG	Z951
Prior MI	I252
CAD	I2510, I25111, I25118, I25119, I252, I253, I254, I2541, I2542, I255, I256, I257, I2570, I25700, I25701, I25708, I25709, I2571, I25710, I25711, I25718, I25719, I2572, I25720, I25721, I25728, I25729, I2573, I25730, I25731, I25738, I25739, I2575, I25750, I25751, I25758, I25759, I2576, I25760, I25761, I25768, I25769, I2579, I25790, I25791, I25798, I25799, I258, I2581, I25810, I25811, I25812, I2582, I2583, I2584, I2589, I259

*We used smart coding where software matches first three main digits of ICD-10-CM coding. Abbreviations: PFO, patent foramen ovale; CAD, Coronary Artery Disease; CABG, Coronary Artery Bypass Graft; PAD, Peripheral Artery Disease; OSA, Obstructive Sleep Apnea; HTN, Hypertension; TIA, Transient Ischemic Attack; CVA, cerebral vascular accident; LOS, Length of Stay; CS, Cardiogenic Shock; APRDRG, All Patients Refined Diagnosis Related Group; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; BAME, Black, Asian and Minority Groups; aOR, Adjusted Odds Ratio; uOR, Unadjusted Odds Ratio; SD, Standard Deviation; PSM-2, Propensity Score Matching STATA module 2; ICD-10-CM, International Classification of Disease, Tenth Edition, Clinical Modification; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Graft; MCS, Mechanical Circulatory Support; AKI, Acute Kidney Injury; CS, Cardiogenic Shock; LOS, Length of Stay; $, Adjust Total Charges; ECMO, Extracorporeal Membrane Oxygenation; HF, Heart Failure; PCA, Percutaneous Coronary Angiography; PCI, Percutaneous Coronary Intervention.

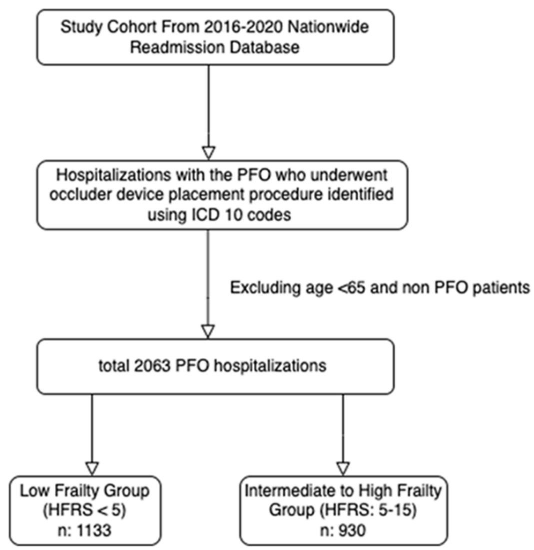

Figure S1. Flow diagram of population and outcomes studied.

Table S2. Definition of major outcomes

Outcome	Definition
In-Hospital Mortality	Death from any cause during the hospital stay
CVA	Any stroke or transient ischemic attack occurring during the admission
LOS	The entire length of stay the patient spent in the hospital during the admission
Cost of hospitalization	The total amount that hospitals billed for their services for the duration of hospitalization

Abbreviations: PFO, patent foramen ovale; CAD, Coronary Artery Disease; CABG, Coronary Artery Bypass Graft; PAD, Peripheral Artery Disease; OSA, Obstructive Sleep Apnea; HTN, Hypertension; TIA, Transient Ischemic Attack; CVA, cerebral vascular accident; LOS, Length of Stay; CS, Cardiogenic Shock; APRDRG, All Patients Refined Diagnosis Related Group; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; BAME, Black, Asian and Minority Groups; aOR, Adjusted Odds Ratio; uOR, Unadjusted Odds Ratio; SD, Standard Deviation; PSM-2, Propensity Score Matching STATA module 2; ICD-10-CM, International Classification of Disease, Tenth Edition, Clinical Modification; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Graft; MCS, Mechanical Circulatory Support; AKI, Acute Kidney Injury; CS, Cardiogenic Shock; LOS, Length of Stay; $, Adjust Total Charges; ECMO, Extracorporeal Membrane Oxygenation; HF, Heart Failure; PCA, Percutaneous Coronary Angiography; PCI, Percutaneous Coronary Intervention.

Table S3. Matching variables used in multivariate logistics regression

Age
Female
Race
Payer Type
Elective
Transfer In
Transfer Out
Hospital Bed Size
Hospital Location
Hospital Region
Year
APRDRG Mortality
APRDRG Severity
HLD
Obesity
Smoker
Prior CABG
Prior MI
Prior PCI

Abbreviations: PFO, patent foramen ovale; CAD, Coronary Artery Disease; CABG, Coronary Artery Bypass Graft; PAD, Peripheral Artery Disease; OSA, Obstructive Sleep Apnea; HTN, Hypertension; TIA, Transient Ischemic Attack; CVA, cerebral vascular accident; LOS, Length of Stay; CS, Cardiogenic Shock; APRDRG, All Patients Refined Diagnosis Related Group; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; BAME, Black, Asian and Minority Groups; aOR, Adjusted Odds Ratio; uOR, Unadjusted Odds Ratio; SD, Standard Deviation; PSM-2, Propensity Score Matching STATA module 2; ICD-10-CM, International Classification of Disease, Tenth Edition, Clinical Modification; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Graft; MCS, Mechanical Circulatory Support; AKI, Acute Kidney Injury; CS, Cardiogenic Shock; LOS, Length of Stay; $, Adjust Total Charges; ECMO, Extracorporeal Membrane Oxygenation; HF, Heart Failure; PCA, Percutaneous Coronary Angiography; PCI, Percutaneous Coronary Intervention.

Table S4. Cardiovascular outcomes of PFO occluder device procedures in IHFS vs. LFS

Outcomes	Low Score	Intermediate-High Score	*p*-Value
Mortality	12.8 (1.1%)	60 (6.5%)	<0.001
AKI	411 (4.1%)	369 (37.9%)	0.350
stroke	33 (2.9%)	88 (9.5%)	<0.001
Post procedural bleeding	11.1 (1%)	14 (1.5%)	0.466
Cardiac Tamponade	12 (1.1%)	<11	0.355

Abbreviations: PFO, patent foramen ovale; CAD, Coronary Artery Disease; CABG, Coronary Artery Bypass Graft; PAD, Peripheral Artery Disease; OSA, Obstructive Sleep Apnea; HTN, Hypertension; TIA, Transient Ischemic Attack; CVA, cerebral vascular accident; LOS, Length of Stay; CS, Cardiogenic Shock; APRDRG, All Patients Refined Diagnosis Related Group; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; BAME, Black, Asian and Minority Groups; aOR, Adjusted Odds Ratio; uOR, Unadjusted Odds Ratio; SD, Standard Deviation; PSM-2, Propensity Score Matching STATA module 2; ICD-10-CM, International Classification of Disease, Tenth Edition, Clinical Modification; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Graft; MCS, Mechanical Circulatory Support; AKI, Acute Kidney Injury; CS, Cardiogenic Shock; LOS, Length of Stay; $, Adjust Total Charges; ECMO, Extracorporeal Membrane Oxygenation; HF, Heart Failure; PCA, Percutaneous Coronary Angiography; PCI, Percutaneous Coronary Intervention.

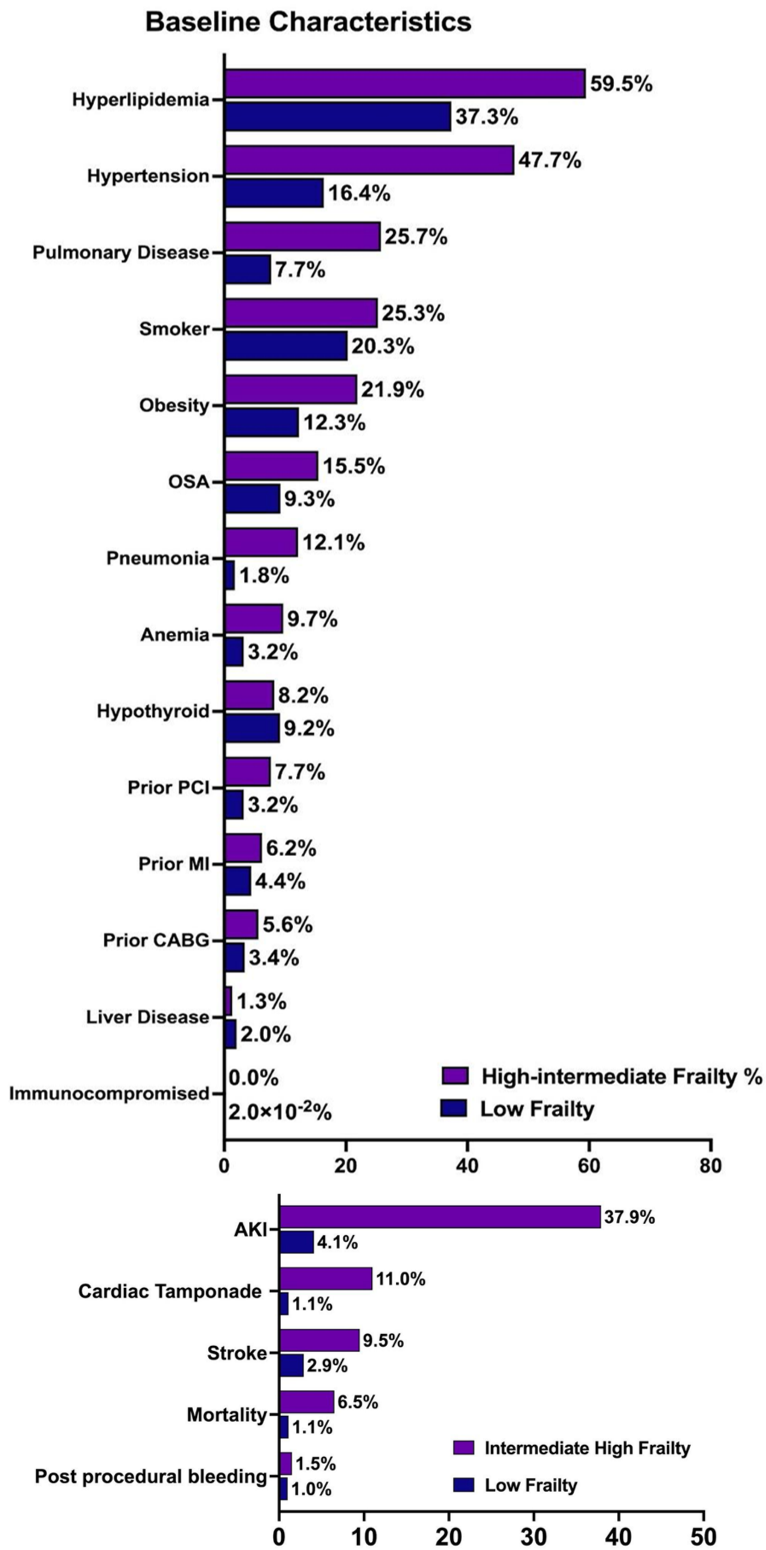

Figure S2. Bar graph comparing percentages of comorbidities based on frailty score in PFO closure patients.

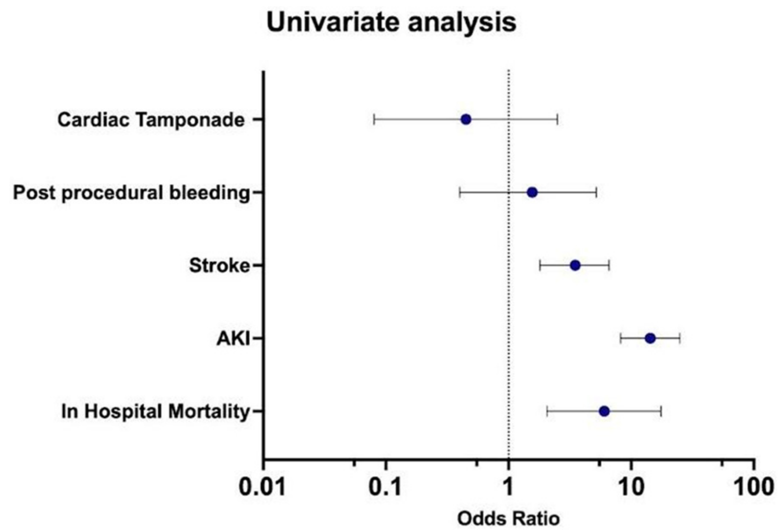

Figure S3. Forest plot depicting the unadjusted outcomes of PFO occluder devise procedures among IHFS vs. LFS.

Table S5. Adjusted and unadjusted outcomes of PFO occluder device procedures in IHFS vs. LFS

Outcome	uOR	lci	uci	*p*-value	aOR	lci	uci	*p-value*
In Hospital Mortality	6.03	2.06	17.5	<0.001	6.3	2.05	19.5	<0.001
AKI	14.3	8.2	24.9	<0.001	17.6	9.5	32.5	<0.001
Stroke	3.5	1.8	6.6	<0.001	3.05	1.5	5.8	<0.001
Post procedural bleeding	1.56	0.4	5.2	0.472	1.89	0.39	8.99	0.419
Cardiac Tamponade	0.45	0.08	2.5	0.368	0.40	0.049	3.25	0.394

Abbreviations: PFO, patent foramen ovale; CAD, Coronary Artery Disease; CABG, Coronary Artery Bypass Graft; PAD, Peripheral Artery Disease; OSA, Obstructive Sleep Apnea; HTN, Hypertension; TIA, Transient Ischemic Attack; CVA, cerebral vascular accident; LOS, Length of Stay; CS, Cardiogenic Shock; APRDRG, All Patients Refined Diagnosis Related Group; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; BAME, Black, Asian and Minority Groups; aOR, Adjusted Odds Ratio; uOR, Unadjusted Odds Ratio; SD, Standard Deviation; PSM-2, Propensity Score Matching STATA module 2; ICD-10-CM, International Classification of Disease, Tenth Edition, Clinical Modification; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Graft; MCS, Mechanical Circulatory Support; AKI, Acute Kidney Injury; CS, Cardiogenic Shock; LOS, Length of Stay; $, Adjust Total Charges; ECMO, Extracorporeal Membrane Oxygenation; HF, Heart Failure; PCA, Percutaneous Coronary Angiography; PCI, Percutaneous Coronary Intervention.

Table S6. 30, 80 and 180 days readmission rates among patients who underwent PFO occluder device procedures in IHFS vs. LFS

Readmission Rates	PFO occluder device procedure		
	Low Score	Intermediate-High Score	*P* value
Readmitted within 30 days	6.3%	8.9%	0.856
Readmitted within 90 days	11.2%	19%	0.705
Readmitted within 180 days	11.4%	16.4%	0.724

Abbreviations: PFO, patent foramen ovale; CAD, Coronary Artery Disease; CABG, Coronary Artery Bypass Graft; PAD, Peripheral Artery Disease; OSA, Obstructive Sleep Apnea; HTN, Hypertension; TIA, Transient Ischemic Attack; CVA, cerebral vascular accident; LOS, Length of Stay; CS, Cardiogenic Shock; APRDRG, All Patients Refined Diagnosis Related Group; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; BAME, Black, Asian and Minority Groups; aOR, Adjusted Odds Ratio; uOR, Unadjusted Odds Ratio; SD, Standard Deviation; PSM-2, Propensity Score Matching STATA module 2; ICD-10-CM, International Classification of Disease, Tenth Edition, Clinical Modification; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Graft; MCS, Mechanical Circulatory Support; AKI, Acute Kidney Injury; CS, Cardiogenic Shock; LOS, Length of Stay; $, Adjust Total Charges; ECMO, Extracorporeal Membrane Oxygenation; HF, Heart Failure; PCA, Percutaneous Coronary Angiography; PCI, Percutaneous Coronary Intervention.

Table S7. Mean and standard deviations for total cost and length of stay of PFO occluder device procedures in IHFS vs. LFS

Outcome	Low frailty	Intermediate-High Frailty	*P* value
Total Cost	$26,542 ($18,227-$44,149)	$46,788 ($28,362-$77,150)	<0.001
Length of stay	1 (1-3) days	9 (5-17) days	<0.001

Abbreviations: PFO, patent foramen ovale; CAD, Coronary Artery Disease; CABG, Coronary Artery Bypass Graft; PAD, Peripheral Artery Disease; OSA, Obstructive Sleep Apnea; HTN, Hypertension; TIA, Transient Ischemic Attack; CVA, cerebral vascular accident; LOS, Length of Stay; CS, Cardiogenic Shock; APRDRG, All Patients Refined Diagnosis Related Group; AHRQ, Agency for Healthcare Research and Quality; HCUP, Healthcare Cost and Utilization Project; NIS, National Inpatient Sample; BAME, Black, Asian and Minority Groups; aOR, Adjusted Odds Ratio; uOR, Unadjusted Odds Ratio; SD, Standard Deviation; PSM-2, Propensity Score Matching STATA module 2; ICD-10-CM, International Classification of Disease, Tenth Edition, Clinical Modification; CKD, Chronic Kidney Disease; CABG, Coronary Artery Bypass Graft; MCS, Mechanical Circulatory Support; AKI, Acute Kidney Injury; CS, Cardiogenic Shock; LOS, Length of Stay; $, Adjust Total Charges; ECMO, Extracorporeal Membrane Oxygenation; HF, Heart Failure; PCA, Percutaneous Coronary Angiography; PCI, Percutaneous Coronary Intervention.