National Estimates for the Percentage of all Readmissions With Demographic Features, Morbidity, Overall and Gender-specific Mortality of Transcutaneous vs Open Surgical Tricuspid Valve Replacement/Repair

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Running title: Demographics and Outcomes of TTVR vs Open TVR

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Abstract:

Aims: To determine national estimates for the percentage of all readmissions with demographic features, length of stay, cost analysis, comorbidities, overall and gender-specific mortality and complications of transcutaneous Tricuspid replacement/repair [TTVR] vs. open surgical tricuspid valve replacement/repair [Open TVR].

Methods: Data was extrapolated from the NRD databases 2015-19. Of the 75,266,750 (unweighted) cases recorded in the 2015 – 2019 dataset, 429 had one or more of the percutaneous approach codes as per the ICD-10 data set, and 10077 had one or more of the open approach codes.

Results: Overall, the number of cases performed each year through open TVR was higher than TTVR, but there was an increased trend towards the TTVR every passing year. TTVR was performed more in females and advanced age groups than open TVR. The length of stay and cost was lower in the TTVR group than in open TVR. Patients undergoing TTVR had more underlying comorbidities like CHF, HTN, and uncomplicated DM. Overall mortality was 3.49 % in TTVR vs. 6.09% in open TVR. Gender-specific analysis demonstrated higher female mortality in the open TVR compared to TTVR (5.45% vs. 3.03 %). Male mortality was statistically insignificant between the two groups (6.8%% vs. 4.3%, p-value 0.15%). Patients with TTVR had lower rates of complications than open TVR, except for arrhythmias, which were higher in TTVR. Patients undergoing open TVR required more intracardiac support, such as IABP and Impella, than TTVR.

Conclusion: Transcatheter tricuspid valve replacement/repair is an emerging alternative to open surgical repair/replacement in patients with tricuspid valve diseases, especially tricuspid regurgitation. Despite having more underlying comorbidities, the TTVR group had lower in-hospital mortality, hospital cost, length of stay, and fewer complications than open TVR.

Introduction:

Recent data demonstrates that TV pathology especially tricuspid regurgitation (TR) is associated with poor long-term survival if left untreated [1]. Intervention on diseased Tricuspid valves, whether open or trans-catheter, has shown to improve the quality of life and severity of the valvular disease in these patients [2]. Tricuspid stenosis is uncommon and accounts only for 2.4% of tricuspid valve diseases [3,4] but Tricuspid regurgitation is very common and it affects > 1.6 million people in United States and > 70 million people worldwide [5]. The causes of primary TR include rheumatic heart disease, direct valvular injury during procedures, infective endocarditis, and connective tissue disorders [6]. Secondary TR is often functional from right ventricular dilatation secondary to left-sided heart diseases or diseases of the pulmonary system with normal tricuspid valve leaflet anatomy [7]. Tricuspid stenosis (TS) is rare and usually is due to congenital or acquired diseases affecting less than 1% of the general population in the developed world due to a decrease in the prevalence of rheumatic heart diseases [8]. Data from European Society Of Cardiology demonstrates that Surgical intervention is recommended for severe symptomatic TR and severe symptomatic TS either alone or at the time of surgery for left-sided valvular heart diseases [9]. Due to high surgical mortality associated with these valvular interventions, medical management was preferred in the past over surgery in the vast majority of these patients [10]. However, there has been a recent increase in trans-catheter tricuspid valve interventions for severe symptomatic tricuspid valvular diseases, especially in patients at higher risk with isolated tricuspid valve disease [11,12]. These interventions did show an improvement in functional status and reduction in severity of valvular disease and mortality [13,14]. Although, we have seen significant advances in trans-catheter treatments for mitral and aortic valves, transcatheter interventions for tricuspid valve are still in the developmental phase [15]. There is also limited data on head-to-head comparison of transcatheter vs. open tricuspid valve interventions. Therefore, we sought to use the Nation-wide readmission data base dataset to identify for the first time ever, the demographic features including morbidity and mortality analysis of trans-catheter vs. open surgical TV interventions.

Materials and Methods:

We used the NRD dataset from years 2015 – 2019 was used for this research project. NRD is a publicly available data sponsored by Agency for Healthcare Research and Quality. The database was developed for the HCUP [healthcare cost and utilization project] and it houses data on 35 million annual weighted discharges from around 28 States. Each patient is assigned a unique identifier code to trace readmissions within specific calendar year. Given the deidentified nature of the database, Institutional Review Board approval and Informed Consent were not required for this study. For each of the variables of interest, we calculated the Weighted Mean or Percentage, and Weighted Standard Error (SE), within each subgroup. Subgroups were cases with the Percutaneous Approach, cases with the Open Approach, or cases with neither. Z-Test Calculator was used to produce a p-value comparing the Percutaneous to Open Approach on the variables of interest. Of the 75,266,750 (unweighted)

cases recorded in the 2015 – 2019 dataset, 429 had one or more of the percutaneous approach codes as per ICD-10 data set, and 10077 had one or more of the open approach codes.

Results:

Baseline Characteristics of Patients:

Data on demographics and baseline co-morbidities demonstrated significant differences between the two groups as shown in table **[Table 1].** Patients undergoing open TVR were relatively younger as compared to TTVR group [mean age 40.8 vs 57.8 years, p-value <0.001] but there were more females in the TTVR group[66.04% vs 55.20%, p-value <0.001]. Data also revealed that patients in TTVR group were significantly sicker with more comorbidities as shown below. The percentage of CHF, uncomplicated HTN, OSA and uncomplicated DM respectively was 75.43%, 61.16%, 16.1% and 8.74% in the TTVR group as compared to 53.48%, 45.53%, 7.9% and 5.41% in the open TVR group**[Table 1].** In contrast, complicated DM and complicated hypertension was higher in the open TVR group[0.83% and 17.38% vs 0% and 11.03%]. Patients in the TTVR group also had a trend towards higher prevalence of COPD but data was not statistically significant[19.9 vs 16.6, p-value 0.1089].

National Estimates for Percentage of All Readmissions:

Of the 75,266,750 total cases, 429 underwent TTVR, and 10077 underwent open TVR. Although overall, the number of cases performed each year through open TVR was higher than TTVR, there was an increased trend towards the TTVR with every passing year (except for a small decrease in 2016) as shown in **[Table 2].**

In hospital outcomes:

Among our patient population, the overall mortality was 3.49 % among the TTVR group vs. 6.09% in open TVR. Gender-specific analysis did demonstrate a higher female mortality in the open TVR as compared to TTVR group (5.45% vs 3.03 %, p-value 0.023). There was however, no statistical difference in mortality among males (6.8%% vs 4.3%, p-value 0.15)**[Table 3].** Overall length of inpatient stay was also more than double in open TVR as compared to TTVR group (23.07 vs 9.8 days, p-value <0.001) **[Table 3].** Cost analysis among the cases from the year 2019 (n=2471 open TVR, n=150 TTVR) demonstrated significantly higher mean costs in the open group vs TTVR. (mean 509107$ versus 308394) respectively (**Table 3**).

Complications:

Overall, patients in open TVR group had more complications as compared to TTVR group. The incidence of Cardiopulmonary Arrest was 2.27% in open TVR vs 1.05% in TTVR group. There was also an increased incidence of ARDS in the open TVR group (0.72% vs 0%, p-value <0.001). Interesting, no ARDS cases were reported in the TTVR group as shown in **[Table 4].** ECMO requirements, however were almost similar in both groups(0.75% vs 0.70% in open TVR vs TTVR, p-value 0.907). In regards to major bleeds and blood loss anemia, data showed almost equal incidence in both groups [4.47% vs 4.2% and 1.2% vs 1.01% in open TVR vs TTVR, p-value 0.83 and 0.56 respectively].

A higher percentage of patients in the open TVR group required permanent pacemaker placement as compared to TTVR (12.7% vs 4.12%, p-value <0.001). Similarly, there was an increased incidence of pericardial effusion and cardiac tamponade in the open TVR population as compared to TTVR population (8.3% vs 1.1% and 1.9% vs 0.2% , p-value <0.001). Patients in the open TVR group also required more mechanical support as compared to TTVR group [IABP: 4.7% vs 1.6%, p-value < 0.001, LVAD: 1.8% vs 0.46% , p-value <0.001]. Data on requirement for Impella support was non-significant between the two groups but there was an increased trend noted in the Open group [0.5% vs 0.19%, p-value 0.119) as shown in **[Table 4].** Patients in open TVR also had more Infective Endocarditis and a higher incidence of stroke as compared to TTVR group (25.04% vs 3.5 % and 1.4% vs 0.57, p-value <0.001 and 0.037 respectively). However, patients in the Trans-catheter group were found to have more post-op arrhythmias than in the open group (76.27% vs 62.2%, p-value <0.001). The incidence of para-valvular leak was also higher (2.3%) in the TTVR group as compared to 0.56% in open TVR (p-value 0.035).

Discussion:
Our analysis revealed that although the number of Trans-catheter interventions were significantly low as compared to open surgery but there was an increasing trend towards minimally invasive approach with each passing year (except for a small decrease in 2016). Patients in the trans-catheter group were also older and more sick which could explain the relative tendency to shift away from conventional surgery due to a higher risk of complications. Another important finding was that trans-catheter interventions were mostly performed in patients with isolated TR (11.17% vs 2.9%, p-value <0.001) as compared to conventional surgery. This is understandable as open surgery usually involves younger people with congenital heart disease with associated structural or valvular abnormalities whereas TR in old age is usually secondary to annular dilatation and may or may not be associated with other cardiac disease **[16, 17].**

To our knowledge, this is the largest and first ever study comparing in-hospital outcomes and national readmission percentages of TTVR vs. open TVR in the American population. The major findings of our study are: An increased trend towards trans-catheter tricuspid interventions as compared to open surgery in years 2015-19, with a significantly lower overall and female mortality as compared to the open group. Trans-catheter approach was also deployed in relatively older patients as compared to open surgery, majorly for secondary TR likely secondary to annular dilation. It was also cheaper, with a shorter length of stay, hospitalization cost, and less complication rates.

The two common pathologies of the Tricuspid valve are regurgitation and stenosis. Tricuspid regurgitation is the more common pathology as compared to stenosis. The prevalence of TR increases with age, and it is also more prevalent in females **[18].** Its management depends on the severity and etiology (primary vs. secondary) of the disease. Mild to moderate TR can be managed medically, while severe TR is managed with either surgical or trans-catheter intervention. As per the American College of Cardiology/American Heart Association joint Committee on clinical practice guidelines favours surgical repair over valve replacement if possible **[19].** The choice of specific surgical technique depends on the stage of TR. Ring annuloplasty with prosthetic rings is usually performed at the mitral or aortic valve surgery in

patients with mild to moderate TR with TA dilation and no significant tethering (coaptation height < 8 mm) **[20].** But rigid undersize prosthetic rings may be used in patients with severe TA dilation(> 45mm) without significant leaflet tethering **[21].** However, if valve replacement is indicated then bioprosthetic valves are preferred over mechanical valves due to low risk of thromboembolism. Controversy exists in literature regarding the appropriate timing of intervention for severe TR which is crucial to avoid irreversible damage to the right ventricle and worsening heart failure **[22].** In the past, severe TR was usually medically managed with preload reduction including diuretics due to the high mortality associated with surgical intervention. There has been, however an increasing trend towards surgical repair of symptomatic severe TR, especially during surgical intervention for left-sided valvular heart diseases **[23].** Studies have reported a poor prognosis in these patients if TR is left untreated during intervention for left-sided valvular heart diseases **[24].** The European Society of Cardiology's Valvular Heart Disease Guidelines recommend TV surgical intervention as a class 1C recommendation for symptomatic severe TS (especially during left-sided valve surgery), severe primary TR undergoing left-sided valve intervention, isolated severe primary TR without severe RV dysfunction and as a class 1B recommendation for severe secondary TR undergoing left-sided valve surgery **[25].** Recent studies have shown that Trans-catheter tricuspid valve intervention can be used as an alternative option in select patients deemed surgically poor candidates **[7].** A study performed on trans-catheter tricuspid valve interventions by Taramasso et al. showed that TTVR has low overall mortality and good functional outcomes with reasonable success rate in patients with severe TR **[26].** Another study by Taramasso et al. showed that the all-cause mortality and 1-year rehospitalization were lower with TTVR as compared to medical management in patients with symptomatic severe TR **[27].** Our analysis also demonstrated similar findings with lower mortality and morbidity outcomes with the trans-catheter approach.

We found TTVR being performed more frequently in females and older age populations as compared to open TVR because of the higher prevalence of TR and surgical inoperability in those groups**[18].** There was also a higher prevalence of comorbidities in patients in the TTVR group compared to the open TVR group. The most common comorbidities were congestive heart failure (CHF), diabetes mellitus (DM), and hypertension (HTN). Especially, patients with LVEF < 40%, right ventricular dysfunction and or pulmonary hypertension carry higher a surgical risk and thus may benefit more from TTVR **[28].** It also explains the higher prevalence of heart failure in patients undergoing TTVR in our study.

Prior studies have shown significant morbidity and mortality with surgical interventions for tricuspid valve diseases. Some retrospective studies have reported an in-hospital mortality of 10.9 % and 8.1 % with surgical isolated tricuspid valve replacement and repair, respectively **[29].** This can be as high as ≥ 20-30 % in patients with pre-operative right ventricular dysfunction. Another study showed an in-hospital mortality of 8 % in patients undergoing tricuspid valve annuloplasty, while the mortality was 37 % in cases of reoperation (due to failure) **[30].** The main prognostic factors contributing to mortality post-surgery were the presence of pre-operative right ventricular dysfunction, pre-operative organ dysfunction (for example, renal or liver dysfunction), underlying comorbidities, and reduced left ventricular function **[31].** Late presentation for tricuspid valve surgery itself was a risk factor for higher

mortality **[32].** Our study showed an overall mortality of 3.49 % in TTVR vs. 6.09% in open TVR. Previous studies performed on transcatheter tricuspid interventions have reported varying degrees of mortality. One study reported an in-hospital mortality of 10 % **[33]** while another reported it to be around 13 % **[34].** The mortality in transcatheter interventions depends on whether replacement or repair was done. A study has shown almost no mortality with the repair. The mortality with valve replacement was 5.7 % and 12.5 % with LUX and NAVIGATE valve systems, respectively **[35].** Our study showed low mortality with TTVR despite more underlying comorbidities in that group.

Study by Zack et al. showed that higher hospitalization cost directly correlates with the length of stay, utilization of pacemakers, and in-hospital mortality **[10].** In our study, the cost was higher for patients with open TVR as compared to TTVR, which can be explained by the higher length of stay, higher mortality, and higher incidence of permanent pacemaker placement in the open group. Similarly, the length of stay depends on the approach for TV interventions and pre-operative right ventricular function. Studies have shown an increased length of stay in patients with right ventricular dysfunction at the time of intervention **[36].** A study performed by Fu et al. showed higher rates of cardiopulmonary bypass time, longer ICU stay, and longer ventilation time for patients with TV replacement as compared to repair, **[37]** which can also contribute to the longer length of stay. Our analysis showed that the length of stay in an open TVR was almost double that of TTVR [23.07 vs. 9.8]. A study performed by Buğan et al. found that the average length of stay was 10.7 days in patients with TTVR, which is similar to our study **[14].**

Data shows that during cardiac surgery, around 0.2% to 6% of patients can develop post cardiotomy cardiogenic shock, this is characterized by tissue hypo-perfusion and end-organ damage despite adequate preload **[38].** It is usually treated with vasopressors, ionotropic support, or in some cases, mechanical support such as an intra-aortic balloon pump insertion (IABP). Around 0.5 – 1% of these patients can also develop refractory post-cardiotomy cardiogenic shock not responsive to these measures, in which case, accelerated support such as ECMO is needed **[39,40].** Patients with pre-operative right ventricular dysfunction are at higher risk of requiring intracardiac support, such as IABP and Impella, due to low cardiac output associated with right ventricular dysfunction **[41]**. In our study, patients who underwent open TVR were more likely to require an intra-aortic balloon pump (IABP) and Impella (although statistically insignificant) than TTVR. ECMO support was almost similar in both groups and statistically insignificant. Different studies have shown poor prognosis and higher short and long-term mortality in patients who required IABP or ECMO support after TAVR, **[42]** but there is limited such data on TTVR.

We also found high utilization of permanent pacemakers in patients with open TVR compared to TTVR. Several factors implicated in the requirement of a pacemaker during TV surgery include intra-operative hypothermia, duration of cardiopulmonary bypass, and proximity of the tricuspid annulus to the atrioventricular node **[43].** The main reason for PPM placement is a complete heart block resulting from compression of the AV node by valve frame or ventricular anchors due to its proximity to the septal leaflet of the tricuspid valve **[44].** Other predictors of PPM placement are infective endocarditis leading to AV block and baseline heart rhythm disturbance **[45].** Previous studies have reported similar findings of permanent pacemaker requirement after valvular heart surgery. Two different studies on

clinical outcomes of TV surgery showed that 21 % and 28 % of patients required permanent pacemakers **[46,47].** Our study showed that 12 % of the patients required permanent pacemakers after the open TVR. A study on 3420 patients has reported that 14.1 % of patients underwent permanent pacemaker implantation after transcatheter aortic valve replacement (TAVR) **[48].** Other studies have reported a 9 – 26 % prevalence of permanent pacemaker placement after TAVR **[49,50,51].** But there is limited data on the need for permanent pacemakers after TTVR.

Pericardial effusion is a common complication after open cardiac surgery and can occur in up to 80% of patients **[52].** The exact mechanism for the development of pericardial effusion is unknown, but the mechanical process of surgery and the inflammatory cytokines are thought to play an important role **[53].** Anticoagulation also increases the risk of significant pericardial effusion and the development of cardiac tamponade **[54,55,56].** Our study found that patients with open TVR have a higher incidence of pericardial effusions and cardiac tamponade than TTVR. This is understandable as open surgery by nature is more invasive and results in significant disruption of intra-cardiac environment and homeostasis as compared to the trans-catheter approach. A retrospective observational cohort study on 1460 patients showed that 16 % of patients undergoing heart valve surgery developed significant pericardial effusion requiring drainage **[57]**. A study on isolated tricuspid valve surgery reported that 8 % of patients developed cardiac tamponade after the surgery **[58].** There is, however limited data available on the incidence of tamponade with transcatheter tricuspid valve interventions.

Patients with intra-cardiac valve replacement also have a significant risk of infective endocarditis (IE). This is usually due to the presence of resulting foreign material in the valve, subsequent paravalvular leaks, and damage to the native calcified valves from valve insertion and subclinical thrombosis **[59,60].** Some 10 – 30 % of all infective endocarditis cases are caused by surgical prosthetic valve endocarditis. Numerous studies have shown a 5 – 50 % in-hospital mortality from infective endocarditis post valvular surgery **[61,62].** Our analysis also showed a higher incidence of infective endocarditis in patients with open TVR than in the TTVR group. There is, although limited data in literature on the incidence of IE from trans-catheter tricuspid interventions. A recent review article on TAVRs which is the best studied among Trans-catheter interventions, showed that there was no difference in the incidence of prosthetic valve endocarditis between surgical and transcatheter aortic valve replacement **[63].** Another study from a large multicenter registry showed the 1-year incidence of IE post-TAVR to be 0.50 % **[64].** Further studies, however are needed in our case to elucidate any differences in IE between the trans-catheter and open groups if any.

Stroke is a rare but serious complication after interventions for valvular heart diseases, which increases morbidity and mortality in these patients. Due to the emerging nature of procedures, there is limited data on the risk of stroke with right-sided transcatheter valvular interventions. The available data on transcatheter tricuspid valve interventions have shown the incidence of the stroke to be close to 1 %, but the number of patients included in those studies was low **[26,65]**. Data from interventions for left-sided valvular heart diseases showed a relatively higher incidence of stroke. This could be due to a higher prevalence of atrial fibrillation in left-sided valvular heart diseases or a higher risk of atrial fibrillation from those interventions **[66]**. A multicentric German TAVI registry study showed the incidence of cerebrovascular

events to be 3.2 %, with significantly higher in-hospital and 1-year mortality in patients developing cerebrovascular events **[67]**. The risk of stroke has been reported to be higher with surgical as compared to transcutaneous approaches in those patients **[49,68]**. Our study showed a higher incidence of stroke from open TVR than TTVR. However, more studies will be needed to accurately predict the risk of stroke in tricuspid valvular interventions.

Conclusion:

Transcatheter tricuspid valve replacement/repair is an emerging alternative to open surgical repair/replacement in patients with tricuspid valve diseases, especially high-risk populations with severe tricuspid regurgitation, to improve the quality of life. Our study's analysis of a large pool of NRD data has shown promising trends towards lower morbidity and mortality and lower overall healthcare cost burden with TTVR compared to open TVR.

Limitations:

The administrative data and retrospective observational study design have their inherent limitations. As hospitalizations and not individual patients are represented in the data, there is a potential for overestimating the number of patients. The number of patients with TTVR in our study cohort was much smaller than open TVR, which could potentially have affected the significance of certain comparisons due to low power. However, the considerable sample size obtained from these large databases attenuates most of the limitations.

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Table1: Baseline Characteristics of patients in TTVR vs Open TVR

Variables	Percutaneous Approach	Open Approach	p-value
Age			
Mean year	57.8 (1.2458)	40.8 (1.2752)	<0.001
Gender %			
Females	66 (2.4172)	55.2 (0.6283)	<0.001
Comorbidities %			
CHF	75.4 (2.3292)	53.4 (1.1088)	<0.001
DM - uncomplicated	8.74 (1.5020)	5.41 (0.2946)	0.029
DM - Complicated	0 (0)	0.08 (0.0266)	0.002
COPD	19.9 (1.9635)	16.6 (0.6808)	0.1089
HTN	61.1 (2.8370)	45.5 (1.1936)	<0.001
HTN - complicated	11 (1.5900)	17.3 (0.5095)	<0.001
HTN - Uncomplicated	50.5 (3.0331)	28.9 (1.0479)	<0.001
OSA	16.1 (1.9607)	7.96 (0.3721)	<0.001

- Standard error in parenthesis

Table 2: National Estimate for Percentage of all Readmissions for TTVR vs Open TVR

Year	Percutaneous Approach	Open Approach
2015	$0.0003197 \ (10^{-3.4})$	$0.0147 \ (10^{-1.83})$
2016	$0.0002789 \ (10^{-3.5})$	$0.0144 \ (10^{-1.84})$
2017	$0.0004506 \ (10^{-3.3})$	$0.0148 \ (10^{-1.82})$
2018	$0.0005399 \ (10^{-3.2})$	$0.0143 \ (10^{-1.84})$
2019	$0.0007247 \ (10^{-3.1})$	$0.147 \ ^{-1.83})$

-Standard error in parenthesis

Table 3: In Hospital Outcomes of TTVR vs Open TVR

Variables		Percutaneous Approach	Open Approach	p-value
Mean LOS in days		9.85 (0.7845)	23 (0.4566)	<0.001
Overall Mortality %		3.49 (0.8874)	6.09 (0.3066)	0.0057
	Female Mortality	3.03 (1.0185)	5.45 (0.3812)	0.023
	Male Mortality	4.39 (1.6394)	6.82 (0.4528)	0.1534
Cost in dollars		308394	509107	

-Standard error in parenthesis

Table 4: Complications of TTVR vs Open TVR

Variables	Percutaneous Approach	Open Approach	p-value
Major bleed	4.2632 (1.0269)	4.4781 (0.2580)	0.839
Cardiac arrest	1.0505 (0.4580)	2.7872 (0.1913)	<0.001
ARDS	0 (0)	0.7294 (0.0939)	<0.001
Cardiac Tamponade	0.2127 (0.2113)	1.9164 (0.1504)	<0.001
Pleural effusion	1.1908 (0.5212)	8.3524 (0.3403)	<0.001
Arrhythmias	76.2786 (2.3614)	62.2894 (1.1188)	<0.001
IABP	1.6158 (0.7511)	4.7343 (0.3247)	<0.001
Impella	0.1907 (0.1912)	0.5093 (0.0723)	0.119
ECMO	0.7012 (0.4101)	0.7506 (0.1093)	0.907
Permanent pacemaker	4.1286 (0.9556)	12.7029 (0.5321)	<0.001
Stroke	0.5738 (0.4165)	1.4839 (0.1282)	0.037
LVAD	0.4611 (0.3281)	1.8043 (0.2020)	<0.001
Blood loss anemia	1.0130 (0.4428)	1.2706 (0.1410)	0.568
Infective endocarditis	3.57 (1.0050)	25	<0.001
Paravalvular leak	2.36 (0.8487)	0.56 (0.0798)	0.035

-Data are presented as the weighted percentage with standard error in parenthesis