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Research Article

Risk Factors for Pars Plana Vitrectomy for Endogenous Endophthalmitis

Aditya Uppuluri[1], Marco A Zarbin[1,2] and Neelakshi Bhagat[1,2]*

[1]*Rutgers New Jersey Medical School, Newark, NJ, USA*

[2]*Institute of Ophthalmology and Visual Science, Rutgers New Jersey Medical School, Newark, NJ, USA*

***Corresponding Author:** Neelakshi Bhagat, Institute of Ophthalmology and Visual Science, Rutgers New Jersey Medical School, Newark, NJ, USA.

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Abstract

Purpose: The objective is to identify demographic, ocular, and microbial variables that are associated with an increased risk of undergoing pars plana vitrectomy (PPV) as part of management for endogenous endophthalmitis (EE).

Methods: Using the 2002 - 2013 National Inpatient Survey Database, we performed a cross-sectional observational study of cases of EE. Variables with a $p < 0.05$ on univariate analysis were included in the multivariate regression model. An adjusted alpha-value of 0.00455 (0.05/11) was calculated using the Bonferroni Correction Method.

Results: A total of 2028 cases of EE were identified. Of these cases, 1821 (89.8%) cases occurred in the adult group (AG) (ages 22+) and 206 (10.2%) cases occurred in the pediatric group (PG) (ages 0 - 21). The average age in the AG was 61.9 years, and the average age in the PG was 2.8 years. Men comprised 54.2% of overall cases (61.2% in PG and 53.5% in AG). Of the 2028 cases of EE, 292 (14.4%) cases underwent vitrectomy: 282 (15.5%) were adult cases and 10 (4.9%) were pediatric cases. Through our univariate analysis, we found that age over 22, cataracts, chorioretinitis, retinal detachment, vitreous hemorrhage, panophthalmitis, orbital inflammation, anterior and posterior synechiae, methicillin-sensitive *Staphylococcus aureus* (MSSA) infection, and pseudomonal infection were associated with an increased risk of undergoing vitrectomy for EE; conversely, *E. coli* infection was associated with a decreased risk of undergoing vitrectomy. After multivariate analysis, with Bonferroni Correction to reduce the likelihood of type 1 error, age over 22, retinal detachment, orbital inflammation, synechiae, and MSSA infection remained significant risk factors of undergoing vitrectomy.

Conclusion: In our analysis, only 10.2% of EE cases occurred in the pediatric group. The proportion of EE cases that underwent vitrectomy was higher in adults (15.5%) than in the pediatric (4.9%) group. Statistically significant variables associated with an increase in the likelihood of undergoing vitrectomy were age > 22 years, retinal detachment, orbital inflammation, anterior and posterior synechiae, and MSSA infection. We also noted that *Streptococcal* species, MSSA, methicillin resistant *Staphylococcus aureus* (MRSA), gram negative bacteria, and *Candida* were the most commonly cultured organisms from the blood of EE patients.

Keywords: *Endophthalmitis; Endogenous Endophthalmitis; Vitrectomy; Risk Factors; PPV; Pars Plana Vitrectomy*

Introduction

Infectious endophthalmitis is a devastating intraocular infection that develops most commonly after an intraocular surgical procedure; it may also occur in the setting of trauma or due to hematogenous spread in the setting of sepsis [1-3]. The latter condition, endogenous endophthalmitis (EE), is due to seeding of the eye from an infected extraocular source [2].

Endophthalmitis typically presents with ocular pain, redness, and decreased visual acuity. Clinical ocular exam findings may include peri-orbital edema and erythema, conjunctival injection, chemosis, hypopyon, and/or vitritis [4,5]. Visual acuity outcomes with endophthalmitis range from 20/20 to no light perception (NLP), depending on the virulence and antibiotic sensitivity of the infecting organism, the immune status of the host, the time between inoculation and initiation of treatment, and associated injuries (in the case of trauma) [4-13].

The primary modality of treatment for EE is intravenous antibiotic therapy. In severe cases, treatment may also include: 1) vitreous tap with intravitreal antibiotics or 2) pars plana vitrectomy (PPV) with intravitreal antibiotics. Severely infected eyes with poor visual prognosis (e.g., no light perception) may undergo primary enucleation [14]. Mild cases of EE may be treated with intravenous antibiotics alone. The treatment of endophthalmitis usually is based on the severity of the clinical presentation and is tailored to each individual case.

Aim of the Study

The aim of the paper is to use the National Inpatient Sample Database to identify patients with EE and identify demographic variables, ocular findings, and pathogens that are associated with a greater likelihood of undergoing vitrectomy as part of management.

Methods

This analysis uses the 2002 - 2013 National Inpatient Sample (NIS) Database to identify demographic variables, ocular findings, and microbial factors that are associated with an increased likelihood of undergoing PPV as part of management of EE. The NIS is a collection of databases and software tools that were created as part of the Healthcare Cost and Utilization Project, which was sponsored by Agency for Healthcare Quality and Research. Because of its large sample size and the rarity of EE, the NIS Database provides researchers an effective means of investigating EE.

The International Classification of Diseases, Ninth Revision (ICD-9) codes 360.00 - 360.99, were used to identify cases of endophthalmitis. Because the ICD-9 does not clearly distinguish between exogenous and endogenous endophthalmitis, we assumed that any case of endophthalmitis in the setting of septicemia without evidence of ocular trauma was endogenous; similarly, because ICD-9 only provides information on blood cultures and not on vitreous cultures, we assumed that the pathogen that caused EE is the same as that cultured in the blood. Chi Square Analysis and Fisher's Exact Testing was used to identify demographic differences between cases that underwent PPV and those that did not. The demographic, ocular, and microbial variables listed in table 1 were used in our regression model. Table 2 outlines the ICD-9 codes as they correlate to our ocular and microbial variables. Table 3 shows the results of the Chi Square Analysis; in the table, each cell also has a percentage value that was calculated by dividing the value in the cell by the total number of surgical (n = 292) or non-surgical (n = 1736) cases. Logistic regression was used to determine which variables and findings were associated with an increased likelihood of undergoing PPV. The statistical package IBM SPSS version 23 was used with P-values of less than 0.05 being considered significant. Bonferroni Correction was applied to reduce the likelihood of type 1 error; after Bonferroni Correction was applied, the new alpha value cutoff used for statistical significance was 0.0045 (0.05/11).

Results

We identified 11,619 cases of endophthalmitis. Of these 11,619 patients, we identified 2,028 cases of EE using the assumptions specified in Methods. Of the 2,028 cases, 901 (29 in pediatric group, 871 in adult group, and 1 (unknown age) had documented septicemia with a bacterial pathogen, 58 (4 in the pediatric group and 54 in adult group) had documented septicemia with a fungal pathogen, 35 (1 in the pediatric group and 34 in the adult group) had documented septicemia involving fungal and bacterial pathogens, and 1034 cases had documented septicemia but no documentation of the causative organism.

Table 3 shows a breakdown of the data by demographic variables, ocular findings, and microbial profile and presents the findings of the Chi Square Test. In our analysis, 206 (10.2%) cases of EE occurred in children between the ages of 0 and 21 (pediatric group), and 1821 (89.8%) of cases occurred in individuals over the age of 22 (adult group). In terms of rate of vitrectomy, 10 (4.9%) cases of EE in the

Demographic	Ocular	Bacteria/Fungi
Gender Age	Cataract Chorioretinitis Hemorrhagic and Serous Choroidal Detachment Diabetic Retinopathy Retinal Detachment Iridocyclitis Hyphema Hypopyon Vitreous Hemorrhage Vitreous Inflammation Corneal Ulcer Keratitis Panophthalmitis Orbital Inflammation Phthisis Vascular Disorders of the Iris and Ciliary Body Corneal Edema Synechiae (Anterior and Posterior) Conjunctivitis Orbital Exophthalmos Scleritis and Episcleritis	*Streptococcus* (excluding pneumococcus) *Pneumococcus* MSSA MRSA Gram Negative *E. coli* *Pseudomonas* *H. influenzae* Anaerobic *Salmonella* *Serratia* *Gonococcal* *Candida* *Aspergillus* *Cryptococcus* *Histoplasma* *Coccidioidomycosis*

Table 1: *Demographic, ocular, and blood bacterial culture results used in multivariable regression model for endogenous endophthalmitis.*

Variable	ICD-9 Codes								
Retinal Detachment	36100	36100	36101	36102	36103	36104	36105	36106	36107
	36181	36181	36189	3619	3612				
Diabetic Retinopathy	36201	36202	36203	36204	36205	36206	36207		
Chorioretinitis and Retinochoroiditis	36300	36301	36303	36304	36305	36306	36306	36307	36308
	36310	36311	36312	36313	36314	36315	36320	36321	36322
Hemorrhagic and Serous Choroidal Detachment	36361	36362	36363	36370	36371	36372			
Iridocyclitis	36400	36401	36402	36403	36404	36410	36411	36421	36422
	36423	36424	3643						
Vascular Disorders of Iris and Ciliary Body	36442								
Synechiae	36470	36471	36472	36473	36474	36475	36476	36477	

Hypopyon	36405								
Hyphema	36441								
Cataract	36600	36601	36602	36603	36604	36609	36610	36611	36612
	36613	36614	36615	36616	36617	36618	36619	36620	36621
	36622	36623	36630	36631	36632	36633	36634	36641	36641
	36642	36643	36644	36645	36646	36650	36651	36652	36653
	3668	3669							
Corneal Ulcer	37000	37001	37002	37003	37004	37005	37006	37007	
Keratitis	37020	37021	37022	37023	37024	3708	3709		
Corneal Edema	37120	37121	37122	37123	37124				
Conjunctivitis	37200	37201	37202	37203	37204	37205	37206	37210	
	37211	37212	37213	37214	37215	37220	37221	37222	
	37230	37231	37233	37239	37239	37234	37020	37021	
	37022	37023	37024	37050	37052	37054	37055	37059	
Panophthalmitis	36002								
Orbital Inflammation	37600	37601	37602	37603	37604	37610	37611	37612	37613
Orbital exophthalmos	37621	37622	37630	37631	37632	37633	37634	37635	37636
Scleritis and Episcleritis	37900	37901	37902	37903	37904	37905	37906	37907	37909
Vitreous Inflammation	37929	36012	36004						
Vitreous Hemorrhage	37923								
Septicemia	0031	0223	0380	0381	03810	03811	03812	03819	0382
	0383	03840	03841	03842	03843	03844	03849	0388	0389
	0545	77181	78552	41512	42292	449	65930	65931	99802
	77183	7907							

***Table 2**: List of variables and corresponding ICD-9 Codes.*

	No Surgical Treatment n = 1736	**Surgical Treatment n = 292**	
Variable	**Number of Cases (% of cases out of 1736)**	**Number of Cases (% of cases out of 292)**	**p-Value**
Sex			0.58
Male	946 (54.5%)	154 (52.7%)	
Female	790 (45.5%)	138 (47.3%)	
Age			< 0.001
0-21 years	196 (11.3%)	10 (3.4%)	
22+ years	1539 (88.7%)	282 (96.6%)	
Retinal Detachment			< 0.001
No	1714 (98.7%)	273 (93.5%)	
Yes	22 (1.3%)	19 (6.5%)	

Diabetic Retinopathy			0.46
No	1695 (97.6%)	283 (96.9%)	
Yes	41 (2.4%)	9 (3.1%)	
Chorioretinitis			0.02
No	1702 (98.0%)	280 (95.9%)	
Yes	34 (2.0%)	12 (4.1%)	
Choroidal Detachment			1.00
No	1734 (99.9%)	292 (100.0%)	
Yes	2 (0.1%)	0 (0.0%)	
Iridocyclitis			0.10
No	1698 (97.8%)	281 (96.2%)	
Yes	38 (2.2%)	11 (3.8%)	
Vascular Disorders of Iris and Ciliary Body			1.00
No	1734 (99.9%)	292 (100.0%)	
Yes	2 (0.1%)	0 (0.0%)	
Hypopyon			0.13
No	1730 (99.7%)	289 (99.0%)	
Yes	6 (0.3%)	3 (1.0%)	
Hyphema			0.46
No	1733 (99.8%)	291 (99.7%)	
Yes	3 (0.2%)	1 (0.3%)	
Cataract			0.001
No	1725 (99.4%)	283 (96.9%)	
Yes	11 (0.6%)	9 (3.1%)	
Synechiae			0.002
No	1733 (99.8%)	287 (98.3%)	
Yes	3 (0.2%)	5 (1.7%)	
Corneal Ulcer			0.08
No	1705 (98.2%)	291 (99.7%)	
Yes	31 (1.8%)	1 (0.3%)	
Corneal Edema			0.14
No	1736 (100.0%)	291 (99.7%)	
Yes	0 (0.0%)	1 (0.3%)	
Keratitis			1.00
No	1733 (99.8%)	292 (100.0%)	
Yes	3 (0.3%)	0 (0.0%)	
Conjunctivitis			0.77
No	1699 (97.6%)	283 (96.9%)	

Yes	37 (2.1%)	9 (3.1%)	
Scleritis and Episcleritis			0.54
No	1732 (99.8%)	291 (99.7%)	
Yes	4 (0.2%)	1 (0.3%)	
Orbital Inflammation			0.002
No	1682 (96.9%)	271 (99.7%)	
Yes	54 (3.1%)	21 (7.2%)	
Orbital Exophthalmos			0.54
No	1732 (99.8%)	291 (99.7%)	
Yes	4 (0.2%)	1 (0.3%)	
Panophthalmitis			0.001
No	1704 (98.2%)	276 (94.5%)	
Yes	32 (1.8%)	16 (5.5%)	
Vitreous Hemorrhage			0.03
No	1728 (99.5%)	287 (98.3)	
Yes	8 (0.5%)	5 (1.7%)	
Vitreous Inflammation			0.13
No	1719 (99.0%)	286 (97.9%)	
Yes	17 (1.0%)	6 (2.1%)	
Phthisis			1.00
No	1732 (99.8%)	292 (100.0%)	
Yes	4 (0.2%)	0 (0.0%)	
MSSA			< 0.001
No	1460 (84.1%)	205 (70.2%)	
Yes	276 (15.9%)	87 (29.8%)	
MRSA			0.19
No	1584 (91.2%)	259 (88.7%)	
Yes	152 (8.8%)	33 (11.3%)	
Streptococcus			0.65
No	1595 (91.9%)	266 (91.1%)	
Yes	141 (8.1%)	26 (8.9%)	
Pneumococcus			0.02
No	1711 (98.6%)	282 (96.6%)	
Yes	25 (1.4%)	10 (3.4%)	
Salmonella			0.14
No	1736 (100.0%)	291 (99.7%)	
Yes	0 (0.0%)	1 (0.3%)	
Anaerobes			0.46
No	1733 (99.8%)	291 (99.7%)	

Yes	3 (0.2%)	1 (0.3%)	
Gram Negative Bacteria			0.78
No	1646 (94.8%)	278 (95.2%)	
Yes	90 (5.2%)	14 (4.8%)	
H. influenzae			1.00
No	1734 (99.9%)	292 (100.0%)	
Yes	2 (0.1%)	0 (0.0%)	
E. coli			0.20
No	1682 (96.9%)	290 (99.3%)	
Yes	54 (3.1%)	2 (0.7%)	
Pseudomonas			0.49
No	1702 (98.0%)	288 (98.6%)	
Yes	34 (2.0%)	4 (1.4%)	
Serratia			0.13
No	1730 (99.7%)	289 (99.0%)	
Yes	6 (0.3%)	3 (1.0%)	
Gonococcus			1.00
No	1735 (99.9%)	292 (100.0%)	
Yes	1 (0.1%)	0 (0.0%)	
Candida			0.10
No	1666 (96.0%)	286 (98.0%)	
Yes	70 (4.0%)	6 (2.0%)	
Aspergillus			0.10
No	1727 (99.5%)	288 (98.6%)	
Yes	9 (0.5%)	4 (1.4%)	
Cryptococcus			1.00
No	1733 (99.8%)	292 (100.0%)	
Yes	3 (0.2%)	0 (0.0%)	
Histoplasma			1.00
No	1735 (99.9%)	292 (100.0%)	
Yes	1 (0.1%)	0 (0.0%)	
Coccidioidomycosis			0.14
No	1736 (100.0%)	291 (99.7%)	
Yes	0 (0.0%)	1 (0.3%)	

Table 3: *Chi square test of demographic, ocular, and microbial variables.*

This table shows the Chi Square Test of our demographic, ocular, and microbial variables. Each cell contains a percentage value calculated by dividing the value of the cell by the total n of the surgical or non-surgical column; this n is 292 for the surgial column and 1736 for the non-surgical column.

pediatric group underwent vitrectomy, and 282 (15.5%) cases of EE in the adult group underwent vitrectomy. There was no significant difference in terms of rate of vitrectomy between men and women. Retinal detachment, chorioretinitis, cataracts, synechiae, orbital inflammation, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Pneumococcus*, panophthalmitis, and vitreous hemorrhage were disproportionately more common in the group of cases that underwent vitrectomy as part of management.

Table 4 provides information regarding the demographic, ocular, and microbial variables that were used in the univariate and multivariate regression models. On univariate analysis, age, cataract, chorioretinitis, retinal detachment, vitreous hemorrhage, panophthalmitis, orbital inflammation, MSSA, *Pneumococcus*, and adhesions and disruptions of the ciliary body and iris were significantly associated with an increased likelihood of undergoing vitrectomy; *E. coli* was associated with a decreased likelihood of undergoing vitrectomy. On multivariate analysis, after the Bonferroni Correction was applied to reduce the likelihood of type 1 error, age over 22 years (HR: 3.09 (95% CI: 1.57 - 6.11)), presence of retinal detachment (HR: 4.22 (95% CI: 2.18 - 8.16)), orbital inflammation (HR: 2.34 (95% CI: 1.32 - 4.15)), MSSA (HR: 2.08 (95% CI: 1.55 - 2.79)), and synechiae (HR: 10.50 (95% CI: 2.26 - 48.79)) were associated with a significant increase in the likelihood of undergoing vitrectomy.

Variable	Univariate		Multivariate	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Gender				
Men	1.00	REF	-	-
Women	1.07 (0.84 - 1.38)	0.58	-	-
Age (years)				
0-21	1.00	REF	1.00	REF
22+	3.59 (1.88 - 6.87)	< 0.001	3.00 (1.53 - 5.93)	0.001*
Cataract				
No	1.00	REF	1.00	REF
Yes	4.99 (2.05 - 12.14)	< 0.001	4.11 (1.53 - 11.02)	0.005
Chorioretinitis				
No	1.00	REF	1.00	REF
Yes	2.15 (1.10 - 4.19)	0.026	2.10 (1.05 - 4.22)	0.037
Hemorrhagic and Serous Choroidal Detachment				
No	1.00	REF	-	-
Yes	-	1.00	-	-
Diabetic Retinopathy				
No	1.00	REF	-	-
Yes	1.26 (0.58 - 2.73)	0.56	-	-
Retinal Detachment				
No	1.00	REF	1.00	REF
Yes	5.42 (2.90 - 10.15)	< 0.001	4.21 (2.17 - 8.15)	< 0.001*
Iridocyclitis				
No	1.00	REF	-	-
Yes	1.75 (0.88 - 3.46)	0.11	-	-
Hyphema				
No	1.00	REF	-	-

Yes	1.99 (0.21 - 19.15)	0.55	-	-
Hypopyon				
No	1.00	REF	-	-
Yes	2.99 (0.74 - 12.04)	0.123	-	-
Vitreous Hemorrhage				
No	1.00	REF	1.00	REF
Yes	3.76 (1.22 - 11.58)	0.021	3.32 (1.05 - 10.50)	0.041
Corneal Ulcer				
No	1.00	REF	-	-
Yes	0.19 (0.03 - 1.39)	0.102	-	-
Keratitis				
No	1.00	REF	-	-
Yes	-	1.00	-	-
Panophthalmitis				
No	1.00	REF	1.00	REF
Yes	3.09 (1.67 - 5.70)	< 0.001	2.59 (1.33 - 5.01)	0.005
Orbital Inflammation				
No	1.00	REF	1.00	REF
Yes	2.41 (1.44 - 4.06)	0.001	2.34 (1.33 - 4.15)	0.003*
Phthisis				
No	1.00	REF	-	-
Yes	-	1.00	-	-
Vascular Disorders of Iris and Ciliary Body				
No	1.00	REF	-	-
Yes	-	1.00	-	-
Corneal Edema				
No	1.00	REF	-	-
Yes	-	1.00	-	-
Adhesions/Disruptions of Ciliary Body and Iris				
No	1.00	REF	1.00	REF
Yes	15.10 (2.92 - 78.22)	0.002	13.03 (2.38 - 71.15)	0.003*
Conjunctivitis				
No	1.00	REF	-	-
Yes	1.19 (0.53 - 2.71)	0.67	-	-
Orbital Exophthalmos				
No	1.00	REF	-	-
Yes	1.49 (0.17 - 13.36)	0.72	-	-
Scleritis and Episcleritis				
No	1.00	REF	-	-

Yes	1.49 (0.17 - 13.36)	0.723	-	-
Vitreous Inflammation				
No	1.00	REF	-	-
Yes	2.22 (0.93 - 5.33)	0.07	-	-
Salmonella				
No	1.00	REF	-	-
Yes	-	1.00	-	-
Streptococcal				
No	1.00	REF	-	-
Yes	1.11 (0.71 - 1.71)	0.65	-	-
MSSA				
No	1.00	REF	1.00	REF
Yes	2.25 (1.69 - 2.98)	< 0.001	2.08 (1.55 - 2.80)	< 0.001*
MRSA				
No	1.00	REF	-	-
Yes	1.33 (0.89 - 1.98)	0.16	-	-
Pneumococcus				
No	1.00	REF	1.00	REF
Yes	2.43 (1.15 - 5.11)	0.02	2.65 (1.21 - 5.80)	0.015
Anaerobic				
No	1.00	REF	-	-
Yes	1.99 (0.21 - 19.15)	0.55	-	-
Gram Negative				
No	1.00	REF	-	-
Yes	0.92 (0.52 - 1.64)	0.78	-	-
H. influenzae				
No	1.00	REF	-	-
Yes	-	1.00	-	-
E. coli				
No	1.00	REF	1.00	REF
Yes	0.22 (0.05 - 0.89)	0.03	0.22 (0.05 - 0.94)	0.040
Pseudomonas				
No	1.00	REF	-	-
Yes	0.70 (0.25 - 1.97)	0.50	-	-
Serratia				
No	1.00	REF	-	-
Yes	2.99 (0.74 - 12.04)	0.123	-	-
Gonococcal				
No	1.00	REF	-	-

Yes	-	1.00	-	-
Candida				
No	1.00	REF	-	-
Yes	0.50 (0.22 - 1.16)	0.11	-	-
Aspergillus				
No	1.00	REF	-	-
Yes	2.67 (0.82 - 8.71)	0.11	-	-

Table 4*: Results of univariate and multivariate regression analysis.*

**After the Bonferroni Correction Method was used, the new alpha value cutoff for statistical significance is 0.0045.*

In bold are the variables whose p-values remained significant after the new alpha value cutoff was used.

Table 5 presents a breakdown of our analysis by pathogens suspected to have caused the endophthalmitis in the two different age groups. The five most commonly cultured organisms from the blood were *Streptococcal* species, MSSA, MRSA, Gram Negative Species and *Candida*.

Age					
	0-21 (n = 206)		**22+ (n = 1821)**		
Bacteria	**Vitrectomy (n = 10)**	**No Vitrectomy (n = 196)**	**Vitrectomy (n = 282)**	**No Vitrectomy (n = 1539)**	**Total # of Cases**
Streptococcus	1 (10.0%)	7 (3.6%)	25 (8.9%)	134 (8.7%)	167
MSSA	0 (0.0%)	4 (2.0%)	87 (30.9%)	272 (17.7%)	263
MRSA	0 (0.0%)	3 (1.5%)	33 (11.7)	148 (9.6%)	184
Pneumococcal	2 (20.0%)	1 (0.5%)	8 (2.8%)	24 (1.6%)	35
Anaerobes	0 (0.0%)	0 (0.0%)	1 (0.4%)	3 (0.2%)	4
Salmonella	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1
Gram Negative	0 (0.0%)	6 (3.1%)	14 (5.0%)	84 (5.5%)	104
H. influenzae	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.1%)	2
E. coli	0 (0.0%)	3 (1.5%)	2 (0.7%)	51 (3.3%)	56
Pseudomonas	1 (10.0%)	1 (0.5%)	3 (1.1%)	32 (2.1%)	37
Serratia	0 (0.0%)	1 (0.5%)	3 (1.1%)	5 (0.3%)	9
Gonococcal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1
Candida	0 (0.0%)	3 (1.5%)	6 (2.1%)	67 (4.4)	76
Aspergillus	0 (0.0%)	1 (0.5%)	4 (1.4%)	8 (0.5%)	13
Cryptococcus	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	3
Histoplasma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1
Coccidioidomycosis	1 (10%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Unknown/Non-Bacterial	5 (50%)	167 (85.2%)	104 (36.9%)	758 (46.5%)	1034

Table 5: *Causative pathogens by age and vitrectomy status.*

Table contains microbial profile of each age group. Some cases that features polymicrobial septicemia are also present. One case is not included due to age not being documented.

Discussion

The Endophthalmitis Vitrectomy Study (EVS) evaluated the role of vitrectomy in management of cases of post-operative endophthalmitis [15]. However, prospective, multicenter, randomized trials have not evaluated the role of vitrectomy in cases of EE. Retrospective reviews and case series, however, have been reported. In their 64-case series of eyes presenting with EE, Connell., *et al*. found that vitrectomy was performed in 56 - 57% of bacterial and fungal EE, while cases with negative blood cultures underwent vitrectomy 21% of the time; similar rates of vitrectomy are reported in other case series [16-19]. Of the cases that underwent vitrectomy, Connell and colleagues found that in the bacterial EE group, 38% experienced an improvement in visual acuity from presentation; in the fungal EE group, 47% experienced improvement; and in the no growth group, 40% experienced improvement. Connell., *et al*. concluded that early vitrectomy in cases of bacterial EE and conservative management in cases of fungal EE was appropriate [19]. Other investigators have recommended that due to the particularly aggressive nature of *Klebsiella* species, EE secondary to such pathogens should be treated aggressively with early vitrectomy [20,21]. Furthermore, from their review of existing literature, Jackson and colleagues concluded that patients who underwent vitrectomy were three times more likely to retain useful vision as compared to those that did not undergo vitrectomy, and patients that underwent vitrectomy were three times less likely to undergo evisceration or enucleation [21]. In contrast, Wong., *et al*. concluded from their retrospective review that final visual acuity was unrelated to the use of vitrectomy [22]. The conflicting findings presented in the literature highlight the need for more research to be done to elucidate the precise role of vitrectomy in managing EE.

In our analysis, we found that retinal detachment in the setting of EE was significantly associated with vitrectomy. Retinal detachment has been documented as both an acute and chronic complication of endophthalmitis and as a complication of surgical treatment of endophthalmitis [23-26]. Thus, retinal detachment in cases of endophthalmitis may be identified at presentation, during the surgical procedure, or during post-operative evaluation. Previous research has shown that concurrent retinal detachment in the setting of endophthalmitis portends a poor visual prognosis [27,28]. Foster., *et al.* further found that the virulence of the causative pathogen also plays a role in visual and anatomic outcomes: cases with more virulent organisms were more likely to have a poorer visual prognosis and greater difficulty in achieving anatomic success [27]. The 19 eyes that had retinal detachment and underwent vitrectomy in this study may have presented concurrently with detachment and EE or developed detachment after vitrectomy to treat infection. Patients who undergo vitrectomy for endophthalmitis seem to be at increased risk of retinal detachment [24-26]. The association between vitrectomy for EE and retinal detachment is complicated by possible selection bias: cases of severe endophthalmitis are more likely to undergo vitrectomy than mild to moderate cases of endophthalmitis. For this reason, it is difficult to evaluate the risk of retinal detachment attributable to the vitrectomy as opposed to the risk attributable to the severity of the endophthalmitis.

Another risk factor significantly associated with undergoing vitrectomy that we identified was the presence of orbital inflammation. Orbital inflammation can be a sign of advanced endophthalmitis (panophthalmitis) and thus may serve as a marker of EE severity [29-31]. Rarely, cases of EE may be the result of bacteremia or direct globe penetration due to orbital cellulitis [2]. Although it is a rare finding, the coexistence of endophthalmitis and orbital cellulitis foreshadows a poor visual prognosis [32-34]. Luke and Song presented a case series of seven cases of concurrent EE and orbital cellulitis in which six eyes required enucleation [35]. We suspect that the severity of the concurrent conditions underlies the increased risk of undergoing vitrectomy that was identified in our analysis.

With respect to the microbial profile, we assumed that the agent causing the endophthalmitis was the same as the one causing the bacteremia. The most common positive microbial culture results were MSSA, MRSA, and *Streptococcal* species. Although this finding mirrors reports by other investigators [1,34-37], Ness., *et al.* found that the most common organism causing EE was *Candida albicans* (48.4% of cases) followed by Gram-positive bacteria (35.5% of cases) [39]. While *Staphylococci* and *Streptococci* may be the most commonly cultured pathogens overall, different comorbidities may affect the organisms that are cultured from the eye. In one study, among 18 cases of EE in patients with diabetes and cirrhosis, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were the 2 most commonly cultured organisms, each present in 38.9% of cases [38]. In a study of endophthalmitis secondary to urosepsis, *Klebsiella* species and *Escherichia coli* were the most commonly cultured organisms [39].

In our study, we found that infection due to MSSA was associated with an increased risk of undergoing vitrectomy. Conversely, we found that methicillin-resistant *Staphylococcus aureus* did not confer any additional risk of undergoing vitrectomy. Because the decision to perform vitrectomy depends on the clinical picture, the results of our analysis, with respect to MSSA and MRSA, suggest that MSSA cases in our study may have had a more severe infection requiring more aggressive treatment. However, the literature is not entirely consistent with this conclusion [39]. In their case series of 32 patients with culture-proven *S. aureus* endophthalmitis, Major and colleagues found that vitrectomy was performed more often in cases of MRSA than MSSA (61% vs. 47%). Furthermore, though the results were not statistically significant, they also observed that a larger portion MSSA cases achieved a final visual acuity of 20/400 or better than did MRSA cases (59% vs. 36%) [40]. In another similar study performed at the same institution but evaluating a different timespan, Ashkan., *et al.* and Nishida., *et al.* identified results similar to the ones put forth by Major and colleagues [41,42]. With respect to complications, Ho and colleagues found a high incidence of retinal detachment in their series of MRSA cases [43]. Given what has previously been published in the literature, it is not entirely clear what underlies our finding that MSSA is significantly associated with an increased risk of undergoing vitrectomy.

In our analysis, we found that the presence of synechiae (anterior and posterior) was significantly associated with an increased risk of undergoing vitrectomy for the management of EE. Synechiae are adhesions that may form because of chronic inflammation that is present in the eye [44]. Synechiae represent an increased inflammatory response in the eye.

Lastly, we found that age over 21 was associated with an increased risk of undergoing vitrectomy as part of management of EE compared with patients of age less than 21 years. The reason for the apparent age dependence of risk is not clear, and it may be a spurious result of statistical data analysis. In their series of 13 cases (11 children) of pediatric EE, Murugan., *et al.* found that 10 cases required vitrectomy, and despite early intervention, some eyes had dismal visual outcomes; 5 of the 13 eyes developed phthisis bulbi, and 1 patient (1 eye) died due to systemic complications. Additionally, 5 of the 13 cases occurred in patients less than 8 months of age. Delay in treatment occurs in young children because of the difficulty associated with examining them thoroughly in an outpatient setting. Almost half the children in this study were referred with an incorrect diagnosis of conjunctivitis and uveitis [45]. Conversely, Haruta., *et al.* describe a case of pediatric EE in which a child maintained a visual acuity of 20/40 seven years after undergoing vitrectomy for EE [46]. Other case reports and series present similar outcomes in cases of pediatric EE that have progressed to blindness and phthisis [47-49]. Conversely, in their series of six neonatal cases of endophthalmitis, Basu., *et al.* found that one eye underwent vitrectomy and later developed phthisis bulbi, two eyes recovered with unimpaired vision following systemic antibiotic therapy without intravitreal injections or vitrectomy, and three patients died [49]. EE in the pediatric population is rare and case studies reveal poor outcomes in this population. Our analysis suggests that pediatric patients are significantly less likely to undergo vitrectomy for the management of EE possibly because these cases were deemed too advanced to achieve any benefit from surgical intervention. The rate of primary enucleation in the pediatric group was 0.5% (1/206), and the rate of primary enucleation in the adult group was 1.8% (33/1821).

Limitation of the Study

One limitation of this study is that the data are derived from a database that was not specifically designed for ophthalmology, so we could not analyze the visual acuity and anatomic success in this project. Both endogenous and exogenous endophthalmitis were reported together in this database; we assumed that infectious cases with concurrent septicemia were the endogenous cases. Also, we could not discern from these data if PPV was primary initial treatment or secondary, after failure of bedside vitreous tap and intravitreal antibiotic injection(s). Additionally, documentation of findings in the NIS is often limited by billable codes; for this reason, ocular findings that are not generally billed for are underrepresented in the database. Furthermore, the data present in this database may not be representative of the experiences of individual care centers. Management of endophthalmitis requires clinical judgement, which may vary from provider to provider, which adds variation to the data present in the database.

Conclusion

In summary, analysis of the National Inpatient Sample Database shows that there are multiple demographic and ocular findings that are associated with an increased likelihood of undergoing vitrectomy as part of management of endogenous endophthalmitis.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki. No protected health information was collected through the course of the study.

Statement of Informed Consent

Because this study involved analysis of an existing database that had no patient identifiers, no informed consent was required.

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