

# Factors associated with delayed diagnosis among Filipino pediatric brain tumor patients: a retrospective review

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**Aim:** Determine delayed diagnosis measured by prediagnostic symptomatic interval (PSI) among Filipino pediatric brain tumor patients and identify associated factors. **Methods:** Data was collected retrospectively on Philippine General Hospital pediatric brain tumor patients from 2015 to 2019. PSI was calculated. Associated factors were determined. **Results:** 196 patients were included. Median PSI was 80.5 days. Longer PSI was significantly associated with older age, supratentorial and low-grade tumors, more physician consults prior to subspecialist referral, longer interval from neuroimaging request to facilitation, and those presenting with seizures (11-month delay), poor school performance (1-year delay), behavioral changes (1.3-year delay) and secondary amenorrhea (3-year delay). **Conclusion:** Delayed diagnosis among Filipino brain tumor patients is associated with age, tumor characteristics and symptoms that are uncommon in this condition. Awareness of these symptoms through physician education, close monitoring of patients, early subspecialist referral and better neuroimaging access may lead to earlier diagnosis.

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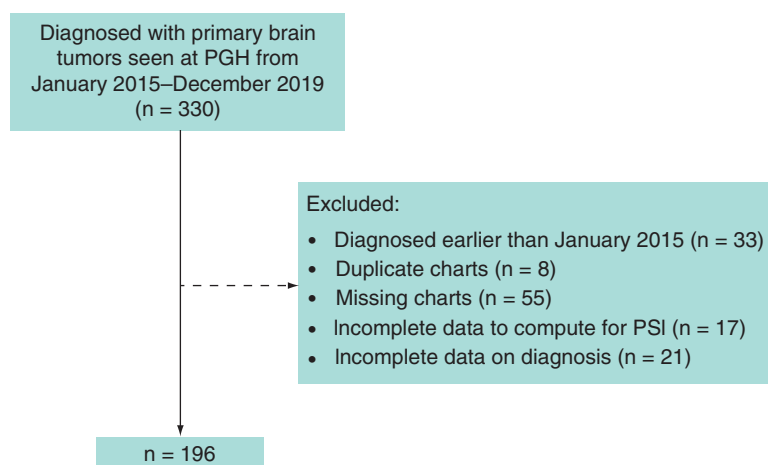
Brain tumors ranked second most common malignancy in children aged 0–14 years old globally [1], with incidence varying from 1.12–5.14 cases per 100,000 persons [2], as well as locally [3]. In the Philippines, the most common tumors were astrocytoma (25.8%) followed by medulloblastoma (23.9%) [4].

Delayed diagnosis of pediatric brain tumors has been documented in various studies and can be devastating to both families and clinicians. Symptomatic deterioration from the first symptom until diagnosis was found in about 50% of the cases [5]. Delays affect treatment and may lead to neurologic, developmental and neuroendocrinologic sequelae [6], impairment of intellectual function [7,8] and even death. This may also cause anxiety and lack of trust in the healthcare system on the part of patients and their families [9].

In brain tumor studies, delayed diagnosis is measured by the pre-diagnostic symptomatic interval (PSI), which is defined as the time from symptom onset to diagnosis. An earlier study done among 316 children diagnosed with intracranial tumors from 1935 to 1959 showed a PSI of >6 months in 50% patients [10]. Despite improvement in evidence, quality and access to diagnostic imaging along the years, improvement in time to diagnosis of pediatric brain tumors has been minimal. Studies in the last decade still showed long median intervals ranging from 30 days to 7.7 months [5,11–17].

Several factors have been associated with delayed diagnosis, including older age [11–13,18–22], presence of comorbidities [5], lower parental education and socioeconomic status [14,23], tumor characteristics [11,13,15,18–22], access to neuroimaging [5,24], and presenting symptoms such as vomiting, headache, ataxia, psychological symptoms and endocrine disturbances [12,13,15–17].

Pediatricians are usually the first physician contact for pediatric patients suspected of brain tumors [20]. Pediatric neurologists and neurosurgeons are usually the second or third contact physician via referrals from primary care physicians. Studies showed longer doctors delay compared with parental delay [11,16,19,25]. In cases with multiple



**Figure 1. Selection of included medical records of pediatric patients diagnosed with primary brain tumors from January 2015 to December 2019.**

PGH: Philippine General Hospital; PSI: Prediagnostic symptomatic interval.

consultations, one of the primary reasons for delay in diagnosis is incorrect diagnosis by primary care physicians such as tonsillitis, gastroenteritis, sinusitis, meningitis or error of refraction [11].

What is unique about the Filipino health-seeking behavior is the tendency to consult traditional healers prior to physicians. In rural areas, traditional healers may be more accessible and less costly than physicians, and patients may seek advice from physicians only if there was no improvement in symptoms. These health-seeking patterns have been observed in local studies on infectious diseases [26,27]. Such health-seeking behaviors among Filipino pediatric brain tumor patients was explored in this study as a contributory factor to diagnostic delay.

Data on delayed diagnosis of pediatric brain tumors is lacking among resource-limited countries like the Philippines. To our knowledge, this is the first local study on this topic. Defining the prediagnostic symptomatic interval among Filipino children will contribute to establishing the burden of delayed brain tumor diagnosis in our setting. Identifying locally relevant predisposing factors will help address parental, doctor and/or health systems-related delays and improve awareness to help promote early recognition of pediatric brain tumors. We aimed to determine delayed diagnosis among Filipino pediatric brain tumor patients, measured by PSI and explore associated factors.

## Materials & methods

### Study design & participants

This retrospective study included pediatric patients aged 2 months to 18 years old diagnosed with a primary brain tumor via neuroimaging and/or histopathology, seen at the Philippine General Hospital (PGH) from January 2015 (computerization of patient to December 2019). Patients diagnosed with congenital brain tumors were excluded. Patients without official imaging results were also excluded.

Using the G\*power software, at least 175 samples were needed for a linear regression analysis with 26 predictor variables (including age, sex, socioeconomic status, highest parental education, tumor characteristics and presence/absence of symptoms), medium effect size of 0.15, 95% confidence interval and 80% power. A total of 196 patients were included after excluding charts of patients diagnosed earlier than 2015, duplicate and missing charts and charts with incomplete data to determine PSI and diagnosis (no official neuroimaging and/or histopathology results) (Figure 1).

### Data collection

We reviewed hospital medical charts, imaging results and histopathology reports. Information gathered included patient characteristics (including comorbid conditions and tumor-related syndromes) and socio-demographics (place of residence, socioeconomic status [28], and parental education); tumor characteristics (location, size measured in volume, grade, histopathology, tumor markers and presence of metastasis); first contact physician, consult with traditional healer, clinical impression prior to brain tumor diagnosis, timing of neuroimaging facilitation; and symptoms at onset, during first physician consult, and upon consultation with neurologist/neurosurgeon. Headaches were further characterized into location, timing, and severity – mild (numerical rating scale or NRS 1–3), moderate (4–7), and severe (8–10); vomiting was characterized into projectile or non-projectile; and seizures were characterized as focal or generalized.

### Prediagnostic symptomatic interval

Overall pre-diagnostic symptomatic interval (PSI) was derived from date of first onset of symptoms to date of diagnosis by neuroimaging. Date of first symptom onset was based on the caregiver's report recorded in the history. If no specific onset date was reported, the most conservative onset was used [21], such as if only the month of symptom onset was recorded, the last day of the month was used as onset date. If only the year was provided in the history, then December 31 of that year was used. Date of diagnosis was defined as the date of the first MRI or CT scan performed. If there was uncertainty regarding brain tumor diagnosis by imaging, the histopathology report date was used as date of diagnosis. PSI was further subdivided into the following [29]:

- A. PSI 1: Symptom onset to first physician consult (parental delay)
- B. PSI 2: First consult to neurologic subspecialist referral (doctors delay)
- C. PSI 3: Subspecialist (pediatric neurologist/neurosurgeon) referral to brain tumor diagnosis (subspecialist delay)

### Data analysis

Demographic and clinical data were presented using descriptive statistics. Quantitative variables were expressed using median and interquartile range (IQR) for non-normally distributed data. Qualitative variables were expressed using frequencies and percentages. Nonparametric tests such as Kendall's tau b, Kruskal-Wallis test and Mann-Whitney U were used to correlate and compare overall PSI among the independent variables, while Wilcoxon signed-rank test was done to compare parental and doctor delay. Linear regression analysis was used to determine predictors of delayed diagnosis. Data transformation was performed to meet the linearity assumption. A p value of 0.05 was used to indicate the level of statistical significance. Missing values were neither replaced nor estimated. STATA version 14 software was used.

## Results

### Patient & tumor characteristics

Table 1 shows the summary of patient and tumor characteristics. The median age at diagnosis was 9 years old. Majority of patients were male (64.3%). Only 7.1% had comorbidities at the time of brain tumor diagnosis, 50% of which had respiratory problems (pneumonia), three had neurodevelopmental comorbidities (autism spectrum disorder, attention deficit hyperactivity disorder), one had ventricular septal defect, one had G6PD deficiency, one had polycythemia vera, and one had cellulitis. Meanwhile, 10 (5%) had tumor-related syndromes, 5 of which had tuberous sclerosis complex, 4 had neurofibromatosis type 2 and 1 had neurofibromatosis type 1. Majority (57%) belonged to the low to lower middle-income cluster. Most of their parents finished high school/vocational courses (44% of mothers and 39% of fathers).

Seventy-five percent (n = 147) had histologic diagnosis, 8.7% were diagnosed by typical imaging findings (n = 17, e.g. diffuse intrinsic pontine glioma, subependymal giant cell astrocytoma) and 12.2% by tumor markers in addition to typical imaging findings (n = 24). An equal number of patients presented with supratentorial and infratentorial tumors. Among the supratentorial tumors (n = 98), the cerebral hemispheres were the most common location (36.7%), while sellar-suprasellar and pineal tumors account for 31.6% each. Meanwhile, majority of infratentorial tumors were posterior fossa tumors (83.7% of infratentorial tumors, 41.8% of all tumors), with medulloblastoma as the most common histopathology (21.9%), followed by low grade gliomas (20.4%), and high-grade gliomas (18.9%). Grade IV is the most common WHO grade (37.8%), followed by grade I (30.1%). Three patients (1.5%) already had metastasis upon diagnosis, all of them diagnosed with medulloblastoma.

### The prediagnostic symptomatic interval

The prediagnostic symptomatic intervals are tabulated in Table 2. The median interval from onset of symptoms to diagnosis (overall prediagnostic symptomatic interval or PSI) was 80.5 days (range 0 to 1815, IQR 31 to 199). The median interval from symptom onset to first consult (PSI 1, or parental delay) was 22 days (range 0 to 1794, IQR 5 to 62), while the median interval from first consult to subspecialist referral (PSI 2 or doctor's delay) was 23.5 days (range 0 to 1464, IQR 5 to 61). There was no significant difference between PSI 1 and PSI 2 (Wilcoxon signed-rank statistic = -0.711, p = 0.477). Median interval between neurologic subspecialty referral and brain tumor diagnosis was 0 days (PSI 3, range 0 to 1471, IQR 0 to 5), since 56.6% of patients (n = 111) consulting the subspecialist already had a brain tumor diagnosis, with neuroimaging showing intracranial tumor upon consult.

Table 1. Patient and tumor characteristics (n = 196).

Age at diagnosis (years)		
Median	9	
Range	1 to 18	
IQR	5 to 13	
Sex	Number of patients	Percentage
Male	126	64.3
Female	70	35.7
Comorbidities and other illnesses	14	7.1
Respiratory	7	3.6
Autism spectrum disorder	2	1
Attention deficit hyperactivity disorder	1	0.5
Ventricular septal defect	1	0.5
G6PD deficiency	1	0.5
Polycythemia vera	1	0.5
Cellulitis	1	0.5
Tumor-related syndromes	10	5.1
Tuberous sclerosis complex	5	2.6
Neurofibromatosis type II	4	2
Neurofibromatosis type I	1	0.5
Income cluster		
Poor	32	16.3
Low to lower middle income	112	57.1
Middle to upper middle income	47	24
Mother's highest educational attainment		
Elementary	12	6.1
High school/vocational	87	44.4
College/post-graduate	56	28.6
Father's highest educational attainment		
Elementary	14	7.1
High school/vocational	78	39.8
College/post-graduate	53	27
Tumor size (volume)		
Median	35.2 cm <sup>3</sup>	
Range	1.5 to 611 cm <sup>3</sup>	
IQR	18.6 to 60 cm <sup>3</sup>	
Tumor location	Number of patients	Percentage
<i>Supratentorial</i>	98	50
Cerebrum	36	18.4
Sellar-suprasellar	31	15.8
Pineal	31	15.8
<i>Infratentorial</i>	98	50
Posterior fossa	82	41.8
Brainstem	16	8.2
Tumor grade		
WHO grade I	59	30.1
WHO grade II	12	6.1
WHO grade III	1	0.5
WHO grade IV	74	37.8
Histopathology		
Medulloblastoma	43	21.9

ATRT: Atypical teratoid rhabdoid tumor; IQR: Interquartile range.

Table 1. Patient and tumor characteristics (n = 196) (cont.).

Low grade glioma	40	20.4
High grade glioma	37	18.9
Germ cell tumors	24	12.2
Craniopharyngioma	14	7.1
Ependymoma	10	5.1
Schwannoma	6	3.1
Pituitary adenoma	3	1.5
ATRT	2	1
<b>Metastasis at diagnosis</b>	3	1.5

ATRT: Atypical teratoid rhabdoid tumor; IQR: Interquartile range.

Table 2. Prediagnostic symptomatic interval.

	PSI 1 (parents delay)	PSI 2 (doctors delay)	PSI 3 (subspecialist delay)	PSI overall
Median	22 days	23.5 days	0 days	80.5 days
Range	0 to 1794 days	0 to 1464 days	0 to 1471 days	0 to 1815 days
IQR	5 to 62 days	5 to 61 days	0 to 5 days	31 to 199 days

IQR: Interquartile range; PSI: Prediagnostic symptomatic interval.

Only 46 (23.5%) of patients were diagnosed within a month from onset of symptoms. Majority were diagnosed within 3-6 months of symptom onset (n = 74, 37.8%), 23 were diagnosed between 2-3 months (11.7%), 25 were diagnosed within 6-12 months (12.8%), and 28 were diagnosed after a year (14.3%), with 10 of these patients diagnosed after 3 years. The characteristics of these patients are seen in Table 3. Eight out of 10 are aged 10 years or older, and majority were diagnosed with benign tumors of the cerebrum and sellar-suprasellar regions. Among patients diagnosed after 1 year, 11 patients (39%) had >1 year symptom onset before first consultation, while 10 patients (36%) took >1 year before subspecialist referral despite early consultation (within 2 months of symptom onset) with first contact physician. Available data on patients who were not diagnosed until after 1 year from symptom onset showed the following reasons: unavailability of neurologist or neurosurgeon in the area (n = 10), wrong interpretation of imaging (n = 4), physician waiting for imaging prior to referral (n = 3), sought consult with multiple physicians for second opinion (n = 3). Three patients already being seen by a pediatric neurologist were diagnosed with brain tumor after 1 year. All three were being treated as epilepsy and imaging was not immediately facilitated.

## Factors associated with delayed brain tumor diagnosis

### Patient & tumor factors

Age had a moderate association with PSI (Kendall's  $\tau_b = 0.27$ ,  $p = 0.027$ ). Older children presented with longer overall PSI compared with younger children. No significant difference in PSI was found in terms of sex ( $p = 0.103$ ), presence of comorbidities ( $p = 0.621$ ), tumor-related syndromes ( $p = 0.154$ ), socioeconomic status ( $p = 0.844$ ) and parental education (maternal  $p = 0.565$ , paternal  $p = 0.558$ ).

PSI was significantly different in terms of tumor location and tumor grade. Supratentorial tumors had longer PSI than infratentorial tumors ( $p = 0.002$ ). In particular, sellar-suprasellar tumors had the longest median PSI of 210 days, while posterior fossa tumors and brainstem tumors had shorter PSI ( $p = 0.020$ ). WHO Grades I and II tumors had longer PSI than WHO Grade IV tumors ( $p = 0.001$ ). Median PSI for Grade I tumors was 153 days, while Grade II tumors had a median PSI of 107 days. Grade III tumors had a median PSI of 28 days, while Grade IV tumors had a median PSI of 61 days. PSI had no association with tumor volume (Kendall's  $\tau_b = -0.004$ ,  $p = 0.941$ ) and did not differ across tumor histology ( $p = 0.060$ ), and presence of metastasis ( $p = 0.837$ ).

### Presenting symptoms

Table 4 shows the frequency of patients presenting with symptoms at onset, during first physician consult and upon subspecialist referral. The most common symptoms were headache (58.7%), vomiting (38.8%), gait imbalance (18.9%), blurring of vision (13.8%) and dizziness (12.8%). Among those with headache, only 26% reported

Patient number	PSI in months	Sex	Age at diagnosis (years)	Tumor location	Histopathology	Initial diagnosis	Symptoms at onset	Number of physicians consulted prior to diagnosis <sup>†</sup>	Neurologic deficits upon neurologic subspecialist consultation
066	38.6	F	10	Sellar-suprasellar	Cranio-pharyngioma	No data	Secondary amenorrhea, headache	2	Bitemporal hemianopsia, decreased visual acuity, exotropia of the left eye
095	36.5	F	9	Cerebrum (left temporal)	Ganglioglioma	Epilepsy	Seizure	2	Slowed speech, slow to respond, fair attention
114	48.9	M	13	Pineal	Mixed malignant GCT	Error of refraction	Blurring of vision, poor school performance	6	Nonreactive pupils, bilateral papilledema, parinaud syndrome
124	60.5	M	14	Sellar-suprasellar	Pituitary adenoma	Primary headache	Headache	3	Left temporal hemianopsia, impaired visual acuity, ilateral lateral rectus palsy
127	38.1	M	4	Sellar-suprasellar	Pilocytic astrocytoma	Error of refraction	Blurring of vision, headache	2	Left homonymous hemianopsia, left extremity drift, left lower extremity clonus, nystagmus
137	48.7	F	13	Cerebrum (right frontoparietal)	Ganglioglioma	No data	Left extremity numbness and weakness	2	Lethargy, bilateral papilledema, left central facial palsy, left hemiplegia
146	49	M	11	Cerebrum (left frontal)	Glioblastoma	No data	Headache, seizure	2	Right lateral rectus palsy, fair gutturals, left hemiparesis, nystagmus
167	45.7	F	18	Cerebrum (right temporal)	Ganglioglioma	Anxiety disorder	Behavioral changes (fear and panic)	4	No deficits, (+) seizures
176	48.7	F	18	Sellar-suprasellar	Germinoma	Unspecified gynecologic dysfunction	Secondary amenorrhea, polydipsia, polyuria	4	Light perception on left, right temporal hemianopsia, optic atrophy
191	49.3	M	13	Posterior fossa	Pilocytic astrocytoma	No data	Headache, vomiting	2	Gait ataxia, dysmetria

Symptoms/signs are listed in the order reported or observed.  
<sup>†</sup>Number of physicians consulted prior to diagnosis excludes neurologic subspecialty consults.  
 F: Female; GCT: Germ cell tumor; M: Male; PSI: Prediagnostic symptomatic interval.

headache upon awakening ( $n = 30$ ), and 23% were occipital in location ( $n = 26$ ). Most had mild (NRS 1–3) headaches at the onset ( $n = 52$ , 45.2%), but majority had severe (NRS 8–10) headaches upon subspecialty referral ( $n = 47$ , 34.3%). Among those with vomiting, only 14% were projectile ( $n = 11$ ). Ten patients (5.2%) presented with seizures, 7 of which were focal seizures. There was an increase in the number of symptoms at onset and at presentation to neurologic subspecialist. At onset and first consult, majority of the patients had at least 2 symptoms (42.3% and 36.2%, respectively). Upon consult with a neurologic subspecialist, 52% had 4 symptoms or more, and only 8.7% were monosymptomatic (Table 5). Fifty-two patients (26.5%) presented with headache and vomiting at the onset while 80 (40.8%) presented with said symptoms upon subspecialist referral. Thirty-seven patients (18.9%) had papilledema, while only 21 patients (10.7%) had the triad of headache, vomiting and papilledema upon referral to subspecialist.

Longer median PSI was significantly associated with the following symptoms: seizures (median PSI of 336 days,  $p = 0.021$ ), poor school performance (median PSI of 792 days,  $p = 0.030$ ), behavioral changes (median PSI of 540,  $p = 0.018$ ), and secondary amenorrhea (median PSI of 365 days,  $p = 0.037$ ). Meanwhile, shorter PSI was significantly associated with vomiting (median PSI of 61,  $p = 0.015$ ). There was no significant difference in median PSI between patients presenting with one, two, three, or more than three symptoms at onset ( $p = 0.494$ ).

### Consultation, referral & timing of neuroimaging

Pediatricians were the most common first contact physicians (68.4%), followed by ophthalmologists (17.9%), as shown in Table 6. No significant difference in median PSI were found across first physician consulted ( $p = 0.054$ ). Four patients (2%) consulted with a traditional healer for their presenting symptoms. Consultation with a traditional

Table 4. Presenting symptoms at onset, during first physician consult, and upon subspecialist consult.

	Median PSI (days)		p-value	Number of patients (percentage) presenting with the symptom			Frequency increase in number of patients presenting with the symptom from onset to subspecialist referral
	Patients with the symptom	Patients without the symptom		At onset	During first consult	Upon subspecialist consult	
Headache	84	78	0.620	115 (58.7)	131 (66.8)	137 (69.9)	23
Vomiting	61	102	0.015	76 (38.8)	94 (47.9)	103 (52.6)	27
Gait imbalance/unsteady gait	61	88	0.132	37 (18.9)	61 (31.1)	77 (39.2)	40
Blurring of vision	92	77	0.119	27 (13.8)	43 (22.4)	61 (31.1)	34
Dizziness	75	83	0.961	25 (12.8)	31 (15.8)	33 (16.8)	8
Diplopia	76.5	83.5	0.918	16 (8.2)	27 (13.8)	40 (20.4)	24
Seizure	336	76	0.021	10 (5.1)	21 (10.7)	28 (14.3)	18
Paresis	62	86	0.312	9 (4.6)	22 (11.2)	37 (18.9)	28
Increased sleeping time	61.5	85	0.192	8 (4.1)	18 (9.2)	30 (15.3)	22
Ocular motility dysfunction	68	86	0.530	7 (3.6)	14 (7.1)	38 (19.4)	31
Poor school performance <sup>†</sup>	792	77.5	0.030	8 (4.6)	8 (4.6)	8 (4.6)	2
Behavioral changes	540	77.5	0.018	5 (2.6)	5 (2.6)	5 (2.6)	0
Secondary amenorrhea <sup>†</sup>	365	77	0.037	5 (13.9)	5 (13.9)	5 (13.9)	0
Polydipsia/polyuria	67	83	0.408	5 (2.6)	5 (2.6)	5 (2.6)	0
Hearing loss	92	78	0.559	3 (1.5)	7 (3.6)	11 (5.6)	8
Numbness	91	78	0.708	3 (1.5)	3 (1.5)	5 (2.6)	2
Facial palsy	63	83		3 (1.5)	7 (3.6)	17 (8.7)	14
Torticollis	63	83	0.082	3 (1.5)	6 (3.1)	7 (3.6)	4

<sup>†</sup> Patients analyzed for these symptoms included only the population at risk. For poor school performance, patients aged 4 years and above (n = 175) were included, based on average age of school entry at 4 years old. For secondary amenorrhea, only females 13 years and above (n = 36) were included, based on average age of menarche for Filipino female of 13 years old. PSI: Prediagnostic symptomatic interval.

Table 5. Number of symptoms at onset, during first physician consult and upon subspecialist consult.

Number of symptoms at presentation	At onset		During first physician consult		Upon neurology/neurosurgery referral	
	Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage
1	69	35.2	48	24.5	17	8.7
2	83	42.3	71	36.2	33	16.8
3	31	15.8	38	19.4	44	22.4
4 or more	13	6.6	39	19.9	102	52

Table 6. First contact physicians.

First contact physician	Number of patients	Percentage
Pediatrician	134	68.4
Ophthalmology	35	17.9
General Doctor	8	4.1
Emergency Medicine	8	4.1
Otorhinolaryngology	4	2
Family Medicine	2	1
Orthopedic	2	1
School Physician	1	0.5
Gastroenterologist	1	0.5
OB Gynecologist	1	0.5

**Table 7. Most common diagnosis prior to brain tumor diagnosis.**

	Number of patients	Percentage
Error of refraction	48	24.5
Primary headache	23	11.7
Gastritis/gastroesophageal reflux	20	10.2
Meningitis	12	6.1
Acute gastroenteritis/dehydration	9	4.6
Epilepsy	8	4.1
Urinary tract infection	7	3.6
Stroke	5	2.6
Vertigo	5	2.6
Psychiatric	4	2

healer did not affect PSI ( $p = 0.613$ ). There is a weak but significant association between PSI and number of different physicians consulted prior to subspecialist referral (Kendall's  $\tau_b = 0.177$ ,  $p = 0.001$ ). Patients who consulted more different physicians prior to neurologic subspecialist referral had longer PSI. Majority of the patients (42.9%,  $n = 84$ ) consulted with one physician prior to neurologic subspecialty referral. The number of consults with said physician, however, cannot be accurately quantified. Meanwhile, 33.2% consulted two different physicians, 24% consulted  $\geq 3$  different physicians prior to being referred. Patients were mostly referred to pediatric neurologists for subspecialty consultation compared with neurosurgery (65.8% vs 34.2%, respectively).

Data on diagnosis prior to brain tumor diagnosis was available for 134 of the charts reviewed (Table 7). Majority were diagnosed with error of refraction ( $n = 48$ , 24.5%), primary headache ( $n = 23$ , 11.7%) and gastroesophageal reflux ( $n = 20$ , 10.2%) prior to brain tumor. Five patients were given two or more diagnoses at first consult. Majority of patients told to have error of refraction were first seen by ophthalmologists (73%), two were seen by otorhinolaryngologists, while the rest were seen by pediatricians. Two patients initially diagnosed with gastroesophageal reflux underwent esophagogastroduodenoscopy showing normal results prior to being worked up for brain tumor.

Imaging is a crucial step in the initial diagnosis of brain tumors. Cranial CT scan was facilitated in most patients ( $n = 129$ , 65.8%), while Cranial MRI was utilized in 67 patients (34.2%). Upon physician's request, patients were able to facilitate neuroimaging within a median of 4 days (range 0 to 535, IQR 1 to 13). Eleven percent of patients ( $n = 21$ ) were able to facilitate neuroimaging after 1 month from request and financial constraint was the most common reason indicated by these patients. Longer PSI had moderate association with longer request to imaging interval (Kendall's  $\tau_b = 0.253$ ,  $p < 0.001$ ).

### Predictors of delayed diagnosis

A multivariate analysis using a linear regression model was done to identify predictors associated with overall delay in diagnosis. Significant predictors are shown in Table 8. Supratentorial tumors, on the average, present with 116 days ( $p = 0.014$ ) risk of delayed diagnosis, while posterior fossa and grade IV tumors, on the average, may be diagnosed 132 days ( $p = 0.041$ ) and 161 days ( $p = 0.002$ ) earlier, respectively, compared with cerebrum and WHO Grade I tumors. Seizures (331 days delay,  $p = 0.002$ ), poor school performance (380 days delay,  $p = 0.008$ ), behavioral changes (500 days delay,  $p = 0.033$ ), and secondary amenorrhea (3-year delay,  $p = 0.021$ ) are significant predictors of delay. Meanwhile, those presenting with vomiting, on the average, may be diagnosed 112 days earlier than those without vomiting ( $p = 0.020$ ).

### Discussion

Our study found that the median interval from onset of symptoms to diagnosis was about 2.7 months. This PSI is longer than majority of the studies done within the last decade [11–16], but shorter compared with others [5,17]. Contrary to other studies that found doctors delay is longer [11,16,19,25], our study found no difference in terms of interval between symptom onset to first consult with a physician (parental delay or PSI 1) and interval between first physician consult to neurologic subspecialist referral (doctor's delay or PSI 2). While majority of patients were diagnosed within 3–6 months of symptom onset, a significant number were still diagnosed after a year. The wide range of PSI in this study can be attributed to inclusion of various tumor histologies and locations. It is



Table 8. Predictors of delayed brain tumor diagnosis.

	Beta coefficient (days)	95% CI	p-value
<b>Tumor characteristics</b>			
Supratentorial	116.10	24.15, 208.05	0.014
Posterior fossa	-132.80	-259.88, -5.71	0.041
WHO grade IV	-161.52	-260.74, -62.31	0.002
<b>Presenting symptoms at onset</b>			
Seizure	331.37	124.37, 538.37	0.002
Poor school performance <sup>†</sup>	380.57	102.35, 658.79	0.008
Behavioral changes	500.07	40.77, 959.37	0.033
Secondary amenorrhea <sup>†</sup>	1122.44	189.69, 2055.19	0.021
Vomiting	-112.85	-207.37, -18.34	0.020

<sup>†</sup> Patients analyzed for these symptoms included only the population at risk. For poor school performance, patients aged 4 years and above (n = 175) were included, based on average age of school entry at 4 years old. For secondary amenorrhea, only females 13 years and above (n = 36) were included, based on average age of menarche for Filipino female of 13 years old.

well established that supratentorial midline and low grade tumors are associated with longer PSI, while posterior fossa and malignant tumors are associated with shorter PSI [11,13,15,18–22,25]. Inclusion of a wide range of tumor histologies in this study may result to the heterogeneity of data on PSI. Other factors also play a role and are further discussed below.

The finding of older patients having longer PSI and younger patients having shorter PSI is consistent with findings of previous cohorts [11–13,18–22]. In fact, 80% of patients with a PSI longer than 3 years were 10 years or older upon diagnosis (Table 3). Studies have hypothesized that shorter PSI for younger children are due to the more invasive nature of CNS tumors in this age group, more regular and routine physician visits in younger children coupled with closer observation by parents and pediatricians and increased intracranial pressure may be observed more frequently in this age group [12,19]. Meanwhile, longer PSI in adolescents may be due to difficulty differentiating true pathology from adolescent behavior and growth changes, less regular physician visits and less reliable self-reporting of symptoms [21].

Tumor characteristics is also a consistent factor affecting PSI in our cohort, as well as in previous cohorts in Europe [13,18,19,22], North America [21,25], Africa [11] and Asia [15,20]. Supratentorial and benign (WHO Grade I) tumors were associated with diagnostic delays compared with malignant (WHO grade IV) and infratentorial tumors. In particular, tumors in the sellar-suprasellar region were shown to take the longest time to be diagnosed among the supratentorial tumors. Histopathologies located in this area revealed mostly benign tumors (42%) such as craniopharyngiomas, pilocytic astrocytomas (optic pathway glioma) and pituitary adenomas. Benign tumors are slow growing and may not cause symptoms until after they have grown significantly large enough to affect vision, gait or cause increased intracranial pressure. Meanwhile, malignant tumors grow aggressively enough to cause bothersome symptoms early on, prompting immediate consultation. CSF blockage caused by tumors in the posterior fossa and brainstem leads to hydrocephalus causing earlier signs of increased intracranial pressure, and lead to earlier consults. Interestingly, several studies have identified delayed diagnosis as a good prognostic factor in childhood brain tumors [22] and earlier diagnosis as a poor prognostic factor [15].

Many of the presenting symptoms of childhood brain tumors found in this study, apart from gait imbalance, are usual symptoms also seen in other common childhood illnesses – headache, vomiting, and blurring of vision. Majority of the previous studies have found headache to be the most common presenting symptom of childhood brain tumors [11–13,15–22,25], regardless of tumor location or histology. In our study, headaches did not have typical red flags (e.g., headache upon awakening). Because these are nonspecific and common symptoms of various childhood illnesses, it might be difficult to pinpoint a brain tumor diagnosis, until these symptoms prove to be persistent, increase in frequency or severity over time, or occur with specific neurologic signs such as facial palsy, paresis or diplopia. Pediatric brain tumor patients are thus prone to initial misdiagnosis and mismanagement, leading to multiple consults as symptoms progress, contributing to delayed diagnosis. Our study found that more physicians consulted was significantly associated with delayed diagnosis, consistent with findings of a Canadian study which showed that only 41% of children were diagnosed within three doctor visits, while 16% required >10 visits before a brain tumor diagnosis was made [25]. Another study found that 50% of children underwent invasive procedures

for other medical conditions before being diagnosed with a brain tumor [30]. Two of our patients underwent esophagogastroduodenoscopy showing normal results, even before cranial imaging was requested. These children already presented with vomiting and gait imbalance at onset, and were eventually diagnosed with a posterior fossa tumor. These findings demonstrate what Sherman *et al.* described as ‘diagnostic imprinting’, wherein an initial diagnosis made causes subsequent physicians to stick to said diagnosis, thus moving away from the consideration of a brain tumor even when evolution of symptoms are present, and may even end up doing unnecessary diagnostic tests. This concept is demonstrated among patients presenting with psychiatric symptoms in their review [31]. Emphasis on educating primary care physicians to avoid diagnostic imprinting is important, and is further discussed later on.

Recognition of signs of increased intracranial pressure is important as death or severe brain damage following this may occur even before the diagnosis of brain tumor is made. In our cohort, only 10% presented with classic triad of headache, vomiting and papilledema. This is in contrast with findings of Dobrovoljac *et al.* [26], which showed that about half of their cohort presented with increased ICP symptoms at onset. These findings demonstrate what Qaddoumi *et al.* conveyed that not all patients with brain tumors present with the classic triad of headache, vomiting and papilledema. Symptoms, especially for low grade tumors, tend to be atypical, varied, wax and wane, and may last for a period of time prior to being diagnosed, especially for low grade gliomas [32]. Furthermore, symptoms may vary in relation to tumor location. Educating physicians that not all brain tumors present with increased ICP symptoms and can present with other atypical symptoms, which will be discussed in the next section, may contribute to earlier diagnosis.

Our study found four symptoms to be predictive of delayed diagnosis while one was predictive of earlier diagnosis. Behavioral changes, poor school performance, and secondary amenorrhea are symptoms which are not commonly observed in children with brain tumors. Endocrine deficits such as secondary amenorrhea, growth retardation, or delayed or precocious puberty may evolve slowly over time, making these symptoms unnoticeable especially if without the presence of more common symptoms. Similar findings were shown in Azizi *et al.* [13]. Despite having other symptoms such as headache, polydipsia and polyuria, a brain tumor diagnosis was explored in our patients who presented with secondary amenorrhea only when they presented with blurring of vision, and increased headache severity, taking about 3 years before neuroimaging was requested.

Behavioral problems are nonspecific symptoms and related to longer PSI. Brasme *et al.* [12] had similar results. In our cohort, five patients presented with behavioral symptoms – 2 presented with aggressive behavior eventually diagnosed with pineal tumor (NGGCT and Germinoma), 1 presented with apathy and decreased verbal output with eventual finding of a thalamic mass but without benefit of histopathology, 1 presented with sudden fear and panic eventually being diagnosed with temporal lobe ganglioglioma for which behavioral symptoms were seizure equivalents, and 1 presented with irritability and agitation who was eventually diagnosed with posterior fossa pilocytic astrocytoma. Four of these patients were initially diagnosed with a psychiatric condition – 3 patients with anxiety disorder and 1 patient with depression. One had undocumented initial diagnosis. Interestingly, only two of these patients had low grade gliomas. On the contrary, Sherman *et al.* showed that low grade gliomas may present with psychiatric and behavioral symptoms, predominantly with eating disorders and related to sellar-suprasellar tumors [31]. This study demonstrates that behavioral symptoms may also be presenting features not just in low grade tumors but also in more aggressive germ cell tumors. Few reports have characterized psychosis [33] with pineal tumors. Meanwhile, fear has been described in temporal lobe seizure presentation [34], while thalamic lesions may present with disturbances in affect and mood [35]. One study postulated that behavioral changes, especially among adolescents, might be part of the changes that they are going through [13]. This may not be readily recognizable by parents or primary physicians alike as a neurologic red flag.

Meanwhile, poor school performance may point toward a neurodevelopmental condition or learning disorder, or may be related to refraction errors, rather than a brain tumor. In our study, patients who presented with poor school performance also had headache and blurring of vision at the onset. Poor school performance might have been attributed to having blurred vision, as majority of these patients were seen by ophthalmologists and treated as error of refraction. It was only until they presented with paresis, cranial nerve palsies and vomiting that prompted neuroimaging request and subspecialist referral.

Interestingly, having seizures at onset is a significant predictor of delayed diagnosis in this study. Seizures are one of the most common causes for emergency consult and hospital admission in children [36]. A study done by Suryaningtyas *et al.* [20] showed that 32% of parents of brain tumor patients seek immediate consult for their children due to seizures. It is a more specific neurologic complaint compared with other symptoms such as vomiting and blurring of vision, and would somehow narrow down differentials to a central nervous system pathology. While

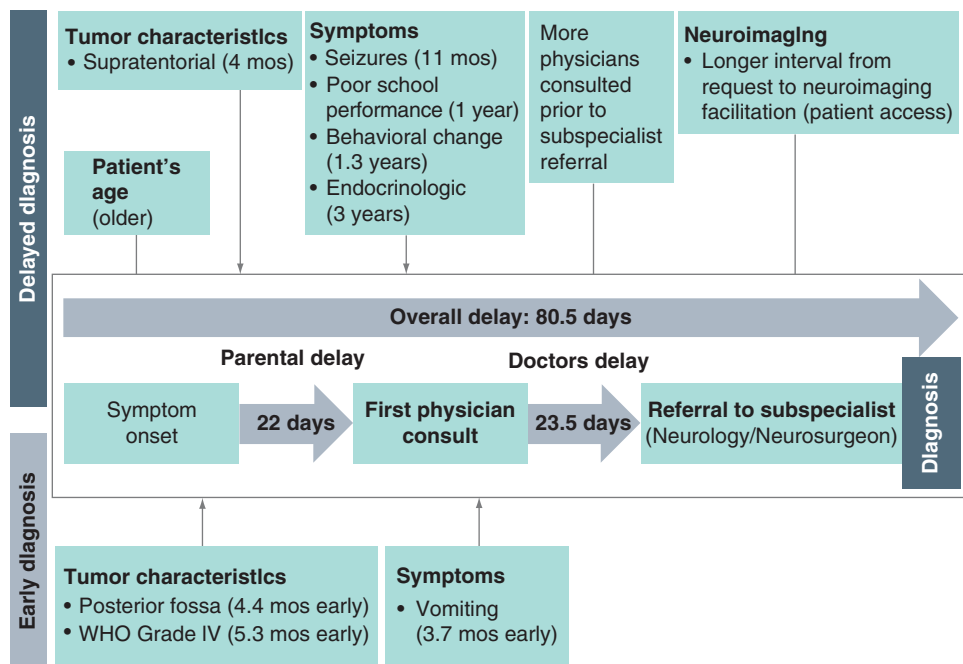
most patients presenting with seizures in our study were brought immediately to the hospital ( $n = 6$ ), 4 patients took more than 9 months prior to consulting. Among those who were seen immediately by a primary care physician, it took more than 3 months for 3 patients to be referred to a subspecialist. Among those who were immediately referred to a neurologist, 3 were being treated as epilepsy for more than a year until neuroimaging was facilitated showing a brain tumor. This finding is reflective of a recent study on low grade gliomas which found a longer median PSI among those patients who presented with seizures compared with those who did not [21]. In children presenting with seizures, especially those presenting with focal seizures, a higher index of suspicion for the diagnosis of brain tumors should prompt both first contact physicians and neurologists alike to request for immediate neuroimaging.

Vomiting on the other hand is a predictor for early detection of brain tumors. Children with brain tumors present with vomiting due to direct stimulation of the vomiting centers in the brainstem by the tumor, and can also be a sign of increased intracranial pressure. Despite being a predictor of early diagnosis, majority of children who presented with vomiting were also the ones who get misdiagnosed at the onset and undergo invasive procedures prior to brain tumor diagnosis. The recurrent episodes and associated dehydration may have prompted parents to consult earlier and more frequently.

Interval from imaging request to facilitation showed a positive association with overall PSI. This echoes the findings of an Israeli study showing that delayed referral to imaging was associated with a 7.7-month delayed diagnosis [5]. Imaging was facilitated earlier among patients who are already in the hospital. Particularly in our institution, cranial CT scan is readily available and affordable for inpatients, since laboratory and imaging studies are subsidized for service patients. However, within the inclusion period of the study, cranial MRI was not always available in our institution and some patients were brought to other facilities for MRI. Cost was a significant factor preventing patients from facilitating neuroimaging immediately, especially among those seen as outpatient. The value of neuroimaging in evaluating children with symptoms of possible brain tumors is controversial. The overall incidence of brain tumors in children with headache as well as other symptoms is low. Physicians may be trapped between requesting for neuroimaging at the onset for early detection versus deferring neuroimaging to observe development of symptoms, since neuroimaging is not without inherent risks (contrast use, sedation, false positive or negative rate) and should also be requested judiciously. Clinicians can be guided in terms of appropriately requesting for neuroimaging and one such guide is the SNOOP mnemonic for identifying headache red flags [37]. Another is Arnautovic *et al.*'s LOW OR PAY [21] (symptoms are **L**ocal/focal, **O**ngoing/long-term, **W**orsening, with **O**ther symptoms present, **R**elapsing/**R**emitting, **P**ersistent, **A**ltering/changing in **A**dolescents or **Y**oung/children) when entertaining a possible diagnosis of low grade glioma.

The first contact physician's role is important in recognizing the signs and symptoms of childhood brain tumors. In our study, the median physician delay is 23.5 days. Majority already presented with at least 2 symptoms upon initial consultation and more than half were given other diagnoses prior to considering a brain tumor. Only 2% of patients consulted traditional healers, which meant that parents tend to consult doctors for such presenting symptoms.

Pediatricians are the first physician contact for children, similar to other studies [11,20], but non-pediatricians were also consulted in this cohort. Majority of the patients who had data on diagnosis were first assessed to have error of refraction by ophthalmologists. Likewise, even neurologic subspecialists may not give a brain tumor diagnosis upon consultation. One patient was treated initially as Guillaine Barre Syndrome, two were given treatment for meningitis, while three patients who were being treated for epilepsy took  $> 1$  year before a diagnosis of brain tumor was made. These findings reflect that of Shay *et al.*'s study showing that delayed diagnosis was associated with examination by ophthalmologists and neurologists [5]. This demonstrates the concept of diagnostic imprinting regardless of which primary care physician or subspecialist sees the patient, and highlights the need for all healthcare practitioners, including primary care physicians, pediatricians, neurologic and non-neurologic specialists, to be knowledgeable about accurate performance and interpretation of the neurologic examination. Improving education on recognition not only of the primary care physician, but also the specialists should be given emphasis. Although early neurologic subspecialist referral is important upon recognition, it should be emphasized that not all patients presenting with a first episode of headache, vomiting or other symptoms discussed should be referred to neurologic subspecialists at onset. At the level of the primary care physician, frequent follow-up and a keener observation of patients presenting with such symptoms, and having a high index of suspicion of brain tumor should be stressed, especially if there is evidence of recurrence, persistence, or progression of such symptoms. The capability of pediatricians and other physicians at the frontline to recognize the common symptoms and signs is particularly needed in rural or remote areas where neurologists or neurosurgeons are not readily available.



**Figure 2. Factors associated with delayed diagnosis in pediatric brain tumors among Filipino children admitted at the Philippine General Hospital.**  
 mo: Month.

Several strategies have been initiated to enhance healthcare providers’ awareness of brain tumor symptoms. In 2011, the UK-based “HeadSmart: Be Brain Tumour Aware” campaign [38] was launched with the aim to raise awareness via a symptom checklist accessible by all physicians and parents alike through their website. The result of this campaign showed reduction in PSI to a median of 6.7 weeks in 2 years. A UK-based, NICE-accredited, evidence-based guideline created in 2010 and revised in 2017 for healthcare professionals recommends that patients should be referred to a pediatric neurologist if symptoms including headache, nausea, vomiting, visual changes or persists, or if physical examination suggests neurologic abnormalities, and to do neuroimaging after four weeks of persistent or recurrent headache or withdrawal in school, after two weeks of persistent nausea or vomiting and/or persistent visual changes [39]. Meanwhile, the SNOOP [37] and LOW OR PAY [21] mnemonics can also be used by clinicians as guide. With this preliminary study on delayed diagnosis, we hope to encourage more studies in order to come up local guidelines to help promote early diagnosis of pediatric brain tumor patients.

Figure 2 represents the findings of this study and how several factors contribute to delayed diagnosis among Filipino children diagnosed with brain tumors.

### Limitations

The dependence of this study on the accuracy and completeness of the patient records is one of the limitations of this study. Measures to ensure extensiveness of data collection were done. Extensive review of inpatient and outpatient charts was done, all databases involving pediatric brain tumor patients were searched, sociodemographic records and narratives of medical social services were likewise explored, and all available radiologic and histopathologic reports were retrieved. However, it cannot be avoided that some data may still be missed, since the study was done retrospectively. Homogeneity of patients in terms of socioeconomic status is a limitation, since the study focused on PGH patients, which represent mainly the lower income spectrum. These limitations do not alter the conclusion of this study.

Parental perspectives such as perceived barriers to seeking consult and facilitating neuroimaging, as well as physician perspectives regarding barriers to early recognition were not included in this study, as we were limited to a retrospective chart review. These may provide additional information in terms of factors affecting delayed diagnosis.

## Conclusion

Delayed diagnosis among Filipino children with brain tumors seen at our institution is primarily associated with older age, tumor characteristics and symptoms that may not be commonly observed in this condition. This study stresses the need for early parental recognition of symptoms that may often be dismissed. Strategies to educate parents include teaching them about what symptoms to watch out for during regular physician visits, as well as advise on early consultation once they notice appearance or changes in such symptoms. First contact physicians should elicit a detailed history, perform and interpret neurologic examination accurately, and be vigilant about these symptoms, carefully and closely monitoring patients with frequent follow-up so that persistence, progression or development of new symptoms will alert them immediately. This may lead to lesser number of different physicians consulted for the same chief complaint and better detection of evolving symptoms. The differential diagnosis of a brain tumor should always be kept in mind when faced with such symptoms. Last, access to affordable neuroimaging should be emphasized, as this also contributes to delayed diagnosis.

## Future perspective

The correlation between delayed diagnosis and survival is beyond the scope of this study and we recommend further studies exploring this association. Parental interviews may also unravel further insights in terms of reasons for parental delays, and a study on primary care physicians' knowledge and practices with regards brain tumors may also give perspective in terms of doctor delays. We also recommend that the impact of delayed diagnosis be investigated separately among specific brain tumor types, especially with the recent changes in classification. Lastly, a similar study exploring delays in diagnosis among pediatric patients with spinal cord tumors may add to the body of knowledge on this topic.

Educating medical students, primary care physicians and subspecialists alike about the signs and symptoms of pediatric brain tumors should be the goal. Medical schools and pediatric residency programs should highlight brain tumor recognition in their curriculum, and emphasize teaching and performing a proper neurologic examination on all children, as pediatricians are at the frontlines in handling these patients. Continuing medical education should allow for more discussion of pediatric brain tumors and recognizing red flags. Delays in pediatric brain tumor diagnosis may be avoided through education, training and establishment of local guidelines.

### Summary points

- To our knowledge, there is no data in the Philippines regarding delayed diagnosis among pediatric brain tumor patients.
- We conducted a single-center retrospective study to evaluate prediagnostic symptomatic interval (PSI) and associated factors among Filipino pediatric patients diagnosed with primary brain tumors in a tertiary government hospital from January 2015 until December 2019.
- The median PSI was 80.5 days, and there was no significant difference between parental delay (median PSI = 22 days) and doctors delay (median PSI = 23.5 days).
- Older age, supratentorial and low-grade tumors are significantly associated with longer PSI. These findings are consistent with previous studies.
- Delayed diagnosis is also observed in patients presenting with behavioral problems (1.3-years delay), poor school performance (1-year delay), and secondary amenorrhea (3-year delay), which are symptoms that may not be commonly observed in this condition. Interestingly, delayed diagnosis was also seen in patients presenting with seizures (11-month delay), and delay is primary related to delayed facilitation of neuroimaging studies.
- There should be vigilance among parents, primary care physicians and subspecialists alike about the symptoms highlighted, keeping a differential diagnosis of a brain tumor in mind.
- Increase in the number of physicians consulted prior to subspecialist referral was also associated with longer PSI. Emphasis should be made on the role of first contact physician in eliciting a detailed history and accurate performance and interpretation of neurologic examination.
- Careful and close monitoring patients with frequent follow-ups should be made so that physicians are immediately alerted of persistence, progression or development of new symptoms or deficits, in order to facilitate earlier subspecialist referral if warranted.
- Delayed facilitation of neuroimaging is also associated with delayed diagnosis and is primarily due to financial constraints. Thus, access to affordable neuroimaging should be emphasized, while employing judicious requests for neuroimaging, as these procedures are not without risks.

### Author contributions

PC Orduña: conceptualized and designed the protocol, facilitated data collection and analysis and interpretation of data; drafted the work and revised it critically for important intellectual content; wrote the manuscript and contributed to the final approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CAP Lubaton-Sacro: gave substantial contributions and inputs to the conception and design of the work and interpretation of results; gave substantial contributions to revising the manuscript critically for important intellectual content; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Ethical conduct of research

Ethical approval was granted by the University of the Philippines Manila Research Ethics Board (UPMREB No. 2020-633-01). A waiver of informed consent was requested from and approved by the UPMREB panel. The study was done retrospectively and involved medical records that are not publicly available and this study did not require direct patient contact. Thus, the research presented no more than minimal risk. The waiver or alteration did not adversely affect the rights and welfare of the participants. In this review of medical records, data anonymity was maintained and information sought was considered non-sensitive (Data Privacy Act of 2012), in accordance to the provisions 17.1–17.3, page 16 and 11.2, page 102 of the National Ethical Guidelines of Health and Health-related Research 2017. No follow-up of patients was done.

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