

## SEASONAL VARIATION OF CEREBRAL VENOUS THROMBOSIS IN BASRA GOVERNORATE

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### ABSTRACT

*Background: cerebral venous thrombosis is an uncommon stroke subtype that affect mainly young age group specially women in reproductive age, although CVT has significant morbidity and mortality, studies regarding its epidemiological data are scares in our country and geographical region including incidence rate, mortality rate and possible seasonality. Aims of study: to determine yearly incidence rate of cerebral venous thrombosis in Basra governorate, age, gender distribution, if there is a possible seasonal variation in incidence and the outcome if patients. Method: cross sectional, retrospective, registry based study was conducted all confirmed CVT cases and their data admitted in neurology ward in Basra teaching hospital and medical and neurosurgical wards in other hospitals between first of January 2010 to end of December 2019 were collected and analyzed. Results: During the 10 years duration between 2010 to 2019, 383 patients were registered with confirmed CVT, 286 were females and 97 were males with 3:1 female male ratio. Mean age of patients were 33 years which was the same for both genders. There was a higher incidence rate in 35-45 years age group with 32.4% of total population. There was no significant seasonal variation in the incidence of CVT in total population and in female gender but male gender showed significant seasonal variation with higher incidence in summer season. Yearly incidence rate of CVT in Basra governorate from 2010 to 2019 were 10.6, 14.3, 25.18, 31, 27.8, 28.35, 21.09, 24.7, 28.55, 27.28 per million per year consecutively with mean 23.9 cases per million per year, with no significant increment or decrement in incidence during the same duration. Mortality rate were 2.3% with no significant gender differences. Conclusion: CVT is a rare stroke subtype with higher incidence in Basra governorate compared to reported incidence globally. it affects mainly younger age group and women, with higher incidence in summer season in male gender and has low mortality rate compared to arterial stroke.*

**Keywords:** Cerebral Venous Thrombosis, Stroke, Seasonal Variation, Cerebral Dural Sinuses, Thrombosis.

## INTRODUCTION

Cerebral venous thrombosis defined as a thrombotic event involve the cerebral dural sinuses with or without cerebral veins. (1) Cerebral sinus thrombosis had different concepts regarding different specialties, for neurology it is regarded as a stroke subtype which involve more young subjects, for hematology it was labeled as a thrombotic event with unusual anatomical site. (1,2)

When comparing CVT versus arterial stroke, a number of differences will be evident: CVT is rare entity which can be readily overlooked, its populations usually including young and specially females in reproductive age, CVT usually has milder onset and less sever presentation than arterial stroke but could present with sever stroke like clinical picture. CVT had variable clinical presentations, it has a lots of risk factors and comorbidities, contrasting those of arterial stroke, also it has a different management approach with anticoagulation as the corner stone for treatment, CVT has better prognosis than arterial stroke.(3)

As stated in recently published study, the incidence of CVT in adults subjects is 13 patient per million a year. Which is much higher than old numbers and this could attributed to recent developing diagnosing facilities including brain-imaging techniques. (4)

A recent study in Portugal showN higher incidence rate of CVT nearly 22 per million per year (5), a higher incidence was also shown in a study conducted in Iran (6). CVT has younger age group populations with usual ages of presentation between 20 to 50 years with less incidence above age 65 years, shows female predominance especially in young females in reproductive age (7). CVT has increased incidence rates in low to middle socioeconomic states with higher fertility rates. (8) Considering the fact that recent developments of diagnostics techniques and increasing awareness of this rare entity, recent studies shown a decrease mortality trend in recent years. (9) CVT have a more varied clinical presentation than other stroke types and hence they are more difficult to recognize. In particular, in the two extremes of their clinical spectrum of severity, CVT may easily missed. CVT patients complaining only of headache may usually have a benign self-limited course. (10)

Predisposing factors of CVT are frequent; generally, they tied typically to the Virchow triad of stasis of blood, alterations in vessel walls, and alterations in the structure of the blood. (11)

Risk factors can be permanent and non-modifiable, such as inherited thrombophilia, or can be conditional or modifiable, like pregnancy, contraceptive pills or infection.(3).

Prothrombotic syndromes are leading predisposing factors for CVT. The most frequent are G20210A prothrombin polymorphism (identified in 6% to 20% of patients with CVT)(12).

The next gender-definite risk factors clarify the increased frequency of CVT in women: oral contraceptives, pregnancy or puerperium, and hormonal replacement therapy. Oral contraceptives are the most frequent risk factor for CVT in women. 54% of women under 50 reported using oral

contraceptives. With women using contraceptive pills have a six times higher risk of having CVT than women who do not use CCP (13). This would lead to a widely variable clinical presentations with different mode of onset and disease chronobiology ranging from hyper acute, stroke like presentation, to subacute and even chronic presentation.(14) Headache, which is the most common presenting symptom (i.e., 75–95% of cases), papilledema, seizures, focal neurological deficits, and altered mental status. Other symptoms described during the onset of CVT include occipital and neck pain that are usually related with sigmoid sinus involvement.(15) CVT must be considered in the differential diagnosis of any patients with idiopathic intracranial hypertension, or in patients presented with severe unexplained headache, and in those who come with stroke syndromes, due to the similar clinical scenarios of these illnesses. (11).

Brain imaging and confirmation of the diagnosis of CVT, demonstration of the thrombus in the brain venous system should done, this could be done using one of these imaging techniques:

1. Magnetic resonance imaging (MRI) with MR venography
2. Computerized tomography (CT) with CT venography,
3. Angiography (11).

Treatment of CVT comprises acute management and post-acute prevention and treatment of CVT consequences. For both of these two sequential stages, complete management should include: management of the concomitant disorders/risk factors; antithrombotic treatment; symptomatic treatment; prevention/treatment of complications; advising on healthy lifestyle and future health conditions.(3)

Reasons for use of anticoagulation treatment in cerebral venous thrombosis are a lot, they include prevent propagation of thrombus to noninvolved veins and Dural sinuses; assist recanalization of occluded veins, and to avoid deep venous thrombosis and pulmonary embolism. (11).

Required antithrombotic therapy in acute stage is heparin (either non-fractionated intravenous heparin or subcutaneous low molecular weight heparin [LMWH], followed by oral anticoagulation with vitamin K antagonists). (3)

### **Endovascular thrombolysis:**

Endovascular thrombolysis, targeting to liquefy the venous clot and reanalyze the obstructed sinus or vein, is an advancement to heparin in severe patients or in cases, which do not improve or worsen in spite of anticoagulation. Catheterization of the sigmoid, transverse, and superior sagittal sinus through the femoral venous or jugular approach followed by local injection of recombinant tissue plasminogen activator (rtPA) or urokinase. Mechanical thrombectomy by disruption (guiding catheter) elimination (balloon catheter), or pull (rheolytic catheter) may also be accomplished. (16)

### **Treatment of intracranial hypertension:**

Diuretics, which inhibit carbonic anhydrase and hence lessen cerebral spinal fluid creation, like acetazolamide or topiramate usually used in order to reduce intracranial pressure to ameliorate headache and avoid visual damage. (17).

Comatose patients must be hospitalized to an intensive care unit for intubation, sedation, mechanical ventilation and intra cerebral pressure monitoring. Osmotherapy (e.g. mannitol) should applied in bolus to decrease intra cerebral pressure.

Decompressive surgery performed to avoid lethal herniation in comatose patients with large parenchymal lesions and impending herniation. Herniation secondary to raised ICP due to unilateral mass effect is the main cause of death in cerebral venous thrombosis (18).

Cerebral venous thrombosis generally has a favorable outcome, but can lead to death or permanent disability. Clinical progression is unpredicted in the early stage after diagnosis. Nearly quarter of cerebral venous thrombosis cases, have a neurological worsening form of declined consciousness, mental status alteration, new seizure, deteriorating of or a new focal deficit, rise in headache severity, or visual loss. Patients with reduced consciousness on admission are more probable to worsen. Seizures are more probable to return in patients who had seizures at beginning and to happen for the first time in patients who had parenchymal injuries. About one third of cases who had neurological worsening will have new parenchymal lesions if neuroimaging is repeated.(14) Approximately 5% of patients die in the acute phase of the disease. (19)

### **Seasonal variation of cerebral venous thrombosis:**

Cerebral venous thrombosis is considered a serious condition affecting mostly young and middle aged adults with high rate of morbidity and mortality specially in women in reproductive age, (20) despite this fact, Epidemiological studies that search for incidence rate of cerebral venous thrombosis and possible seasonality in their incidence is scares.

The seasonal variation of cerebral venous thrombosis has not documented. Only three studies have studied the seasonality of CVT and proposed that the CVT frequency rate could differ by season but the results were inconsistent.(21)

Ferro et al mentioned for the first time on seasonality in the cerebral venous thrombosis incidence and found a unimodal pattern with the peak frequency of the disorder throughout autumn and winter (20)

Stolz et al reported the seasonal variation of CVT onset in a German cohort and found a bimodal distribution with the maximum number of new CVT cases during the summer and winter seasons compared with the spring and autumn months.(22)

Janghorbani Et al reported a statistically significant seasonal distribution with highest number of CVT patients in Autumn in a cohort study in Isfahan.(21).

In this study, we try to estimate the seasonal variation of cerebral venous thrombosis in patients in Basra, with age and gender distribution, yearly incidence rate, the outcome of patients and mortality rate.

## **METHODS**

### **Study design and setting**

A descriptive, retrospective, registry-based study carried out in Neurology ward of Basra Teaching hospital, the only neurology tertiary center in Basra governorate where nearly all cerebral venous thrombosis cases in Basra used to refer to. For being certain not to miss other cases being admitted in other hospital departments, we also searched in medical and neurosurgical wards registries in other hospitals of Basra where cerebral venous thrombosis cases could be admitted.

### **Administrative arrangement**

Necessary permission and clearance obtained from Basra health directorate /Iraq ministry of health to review hospitals medical records, in statistic departments and hospital archives.

### **Study population**

All medical records of cerebral venous thrombosis cases that admitted to neurology ward (Basra teaching hospital and other medical and neurosurgical wards in Basra) in the duration from the beginning of January 2010 to the end of December 2019. All CVT confirmed cases diagnosed using medical history and examination with proper brain imaging including brain MRI, MRV and brain CT all recorded in this study. Special form prepared by researcher for the purpose of data collection, which include the following aspects: Personal characteristics (age, gender); Date of admission; Patient outcome (unknown, improved, died, disabled).

### **Data collection**

Data collected by researcher using special form during the working hours from 12:00 pm to 2.00 pm every Monday and Thursday for 2 hours between the beginning of December 2019 to the end of February 2020 using medical records of medical neurology ward in Basra teaching hospital and records in other hospitals.

### **Inclusion criteria**

We include all records of confirmed cases of CVT during the period from first of January 2010 to end of December 2019, who lived in Basra governorate who admitted for diagnosis and treatment of cerebral venous thrombosis.

### **Exclusion criteria**

Patients admitted to Basra hospitals who lived outside Basra governorate.

Patients with traumatic cerebral venous thrombosis.

### Definition of variables

Seasonal variation: According to world meteorological organization records seasons of year were divided into winter (December, January, February), Spring (March, April, May). Summer (June, July, August), Autumn (September, October, November), frequency of cases was calculated for each season of year. Outcome (unknown, improved, died, disabled).

### Statistical analysis

Analysis of data collected performed using SPSS (Statistical package for social science version 23) program. Frequency of cases in each season were compared together to find any significant seasonal variation in the incidence of cerebral venous thrombosis using one way ANOVA test for comparison. Comparison between frequencies of cases between genders was done using chi square and P value < 0.05 considered significant. Incidence rate calculated manually by dividing number of cases on total population at risk of Basra governorate for each year.

$$\text{Incidence Rate} = \frac{\text{number of cases recorded in specific year}}{\text{total population at risk in the same year}} \times 1000000$$

Denominator of our equation obtained from General Health Directory official records. Then comparison of incidence rate of each year done using Pearson correlation test to identify any significant change in incidence rate during the past 10 years and P< 0.05 considered significant.

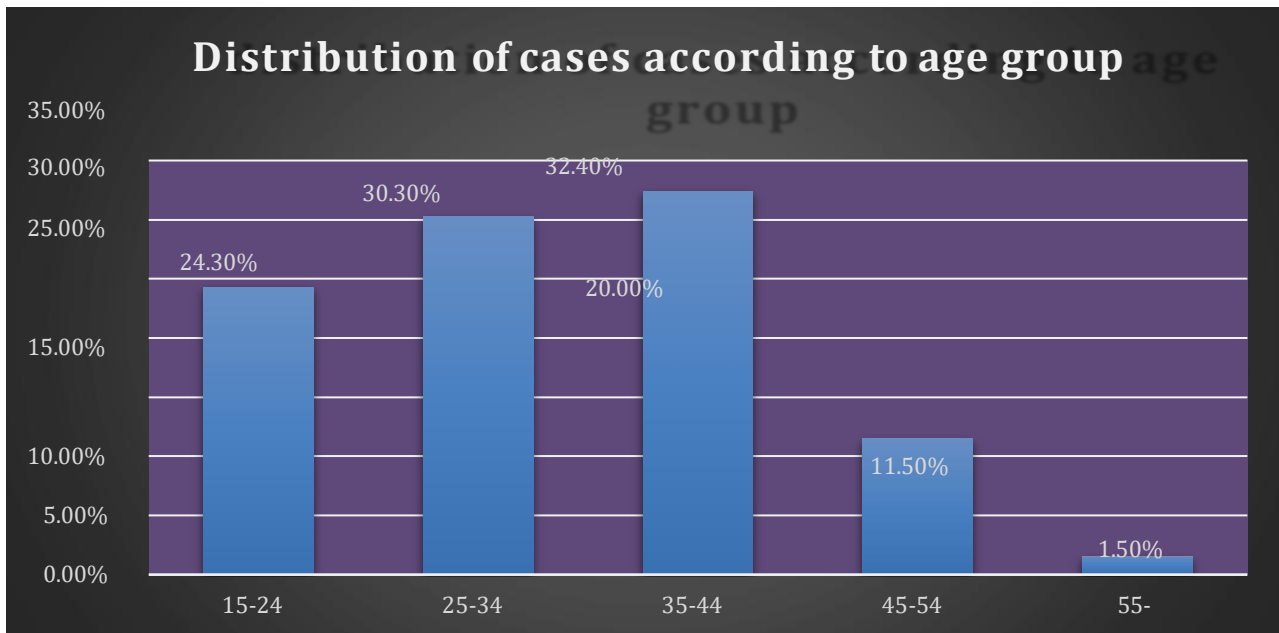
Mortality rate was calculated and comparison between both genders done using chi square.

$$\text{Mortality rate} = \frac{\text{number of total dead patients}}{\text{number of total cases}} \times 100$$

Analysis of possible seasonal variation in mortality rate performed using one-way ANOVA test. All data will present in tables and diagrams.

## RESULTS

In this study, we included 383 patients with confirmed diagnosis of cerebral venous thrombosis who admitted to neurology ward and other wards involving in management of CVT patients from first of January 2010 to end of December 2019. Our sample including 286 female (74.7%) patients and 97 male (25.3 %) patients with male female ratio 1:3. Mean age of patients enrolled in this study was 33 years with youngest age was 16 years and oldest was 60 years with 99% slandered deviation. Mean age for male patients was 33 years, which is the same for total cases and for female mean age of onset. Median age was 34 years for male, 33 years for females and for total cases. (Figure 1)



**Figure 1. Bar chart shows percentage of CVT cases according to each group**

#### Seasonal variation in cerebral venous thrombosis incidence

The frequency of cases collected calculated according to date of onset in the duration between first of January 2010 to end of December 2019 according to seasons. The results illustrated in the following table 1. Analysis of seasonal variation of CVT incidence was done using one way ANOVA test and show no significant seasonal variation between incidence of CVT with P=0.085.

**Table 1: cases distribution according to seasons**

Years	Winter	%	Spring	%	Summer	%	Autumn	%
2010	2	12.5	4	25	6	37.5	4	25
2011	6	27.2	5	22.7	7	31.8	4	18.1
2012	10	27.7	7	19.4	13	36.1	6	16.6
2013	9	19.5	10	21.7	15	32.6	12	26
2014	11	26.2	8	19	12	28.5	11	26.2
2015	9	20.4	14	31.8	14	31.8	7	15.9
2016	10	28.5	9	25.7	11	31.4	5	14.2
2017	12	27.2	11	25	13	29.5	8	18.1
2018	11	22.4	14	28.5	12	24.4	12	24.4
2019	11	22.4	11	22.4	15	30.6	12	24.4
Total	91	23.7	93	24.3	118	30.1	81	21.1

Regarding seasonal distribution according to each gender, the following frequency tables (2 and 3) showed males and females distribution. Statistical analysis of male patient’s distribution on seasons using ANOVA test showed a significant seasonal variation with higher peak of incidence in summer season  $P=0.033$ . Female incidence of CVT showed no statistical significance regarding seasonal variation with  $P=0.208$ .

Table 2: Distribution of male patients according to season

Years	Winter	Spring	Summer	Autumn	Total	%
2010	0	0	1	2	3	3
2011	0	0	2	1	3	3
2012	2	4	4	0	10	10.3
2013	1	3	6	4	14	14.4
2014	2	1	4	4	11	11.3
2015	1	3	2	2	8	8
2016	2	0	4	2	8	8
2017	0	2	5	1	8	5
2018	3	4	4	4	15	15.4
2019	5	4	5	3	17	17.5
Total	16	21	37	23	97	

Table 3. Female patients’ distribution according to seasons.

Years	Winter	Spring	Summer	Autumn	Total	%
2010	2	4	5	2	13	4.5
2011	6	5	5	3	19	6.6
2012	8	3	9	6	26	9
2013	8	7	9	8	32	11.1
2014	9	7	8	7	31	11
2015	8	11	12	5	36	12.6
2016	8	9	7	3	27	9.1
2017	12	9	8	7	36	12.6
2018	8	10	8	8	34	11.9
2019	6	7	10	9	22	7.7
Total	75	72	81	58	286	

Incidence rates

In this study, we calculate the incidence rate for each year manually by dividing the new cases each

year on total population at risk (people aged 15 years and older) multiplied by one million. The highest incidence rate was recorded at 2013 with 31 cases per million, the lowest incidence was recorded at 2010 with 10.6 case per million per year. The mean incident rate during the duration between January 2010 to end of December 2019 was 23.97 case per million per year. Analysis of possible correlation between advance years and incidence rate using Pearson correlation coefficient show a positive correlation (0.611) but statistically not significant (P=0.06). (Table 4)

Table 4. CVT incidence rate each year

Year	Number of cases	Population at risk	Incidence rate (per million)
2010	16	1502873	10.64
2011	22	1533659	14.34
2012	36	1429371	25.18
2013	46	1482101	31
2014	42	1508979	27.83
2015	44	1541977	28.35
2016	35	1658815	21.09
2017	44	1779685	24.7
2018	49	1716010	28.55
2019	49	1761193	27.28
mean			23.97

**Mortality rate**

Patients outcome included 374 cases out of 383 cases (97.7%) recovered and discharged home while nine patients died (2.3%). Regarding gender distribution of mortality 8 patients death were females and one death was male. Statistical comparison between gender mortality using chi square showed no significant difference between fatality in both genders with P=0.985. Analysis of seasonal variation in mortality rate using one way ANOVA test show no statistical significance with P=0.576. (Table 5) (Figure 2)

Table 5. CVT outcome according to gender

Year	Male			Female			Total		
	Recover ed	De ad	Mortalit y rate	Recover ed	De ad	Mortal ity rate	Recover ed	De ad	Mortal ity rate
2010	3			13			16		
2011	3			16	3	6%	19	3	13.6%

2012	10			26			36		
2013	14			32			36		
2014	10	1	10%	30	1	3.2%	40	2	4.7%
2015	8			36			44		
2016	8			26	1	3.7%	34	1	2.8%
2017	8			35	1	2.8%	43	1	2.2%
2018	15			33	1	2.9%	48	1	2%
2019	17			31	1	3.1%	48	1	2%
	96	1	1%	278	8	2.7%	372	9	2.3%

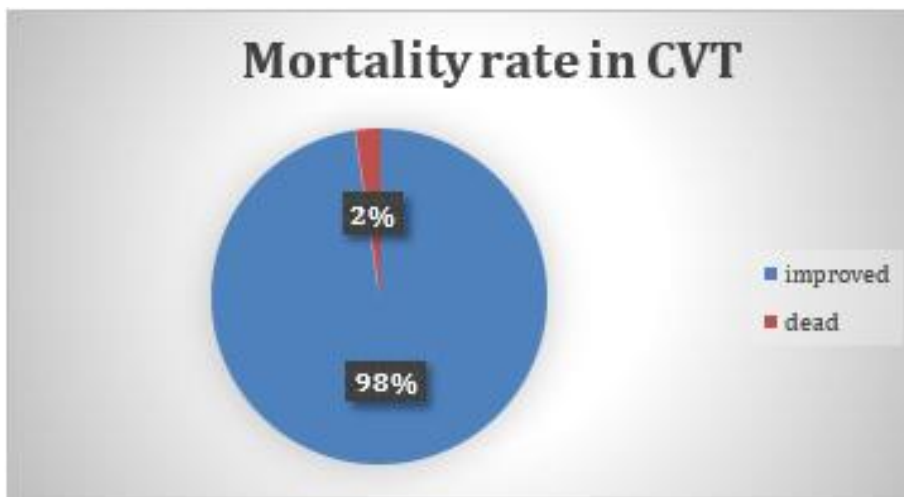


Figure 2. Pie chart shows mortality rate of CVT.

## DISCUSSION

In our study we enrolled 383 patients with diagnosed CVT who were admitted to neurology ward, and medical and neurosurgical wards in Basra teaching hospital and the rest hospitals in Basra.

Patients were divided into 286 females (74.7%) and 97 males (25.3%) with a female male ratio about 3:1 which was the same finding by Coutinho et al (23) who found in a prospective multicentric study in 2009 with 624 cases 75% of theme were females.

The median age of patients who was included in this study was 33 years, median age for females was 33 years and for males was 34 years. this finding was younger than results found by Ferro et al who found a median age of onset 37 years with younger age for female 34 years and older for male 42 years(14), and Coutinho et al who found a mean age of 41 years older than our results with mean age of 33 years (24) in multicentric international study underwent in Europe, t h i s can be explained in by younger age of marriage and pregnancy in our society compared to Europe and younger age of

total population in general with higher exposure to hormonal risk factors at earlier age with their thrombotic complications.

This was also much younger than the mean age for arterial stroke 63.9 years (25) in a study was held in Chungnam China including 12370 patients, this could be explained by the different risk factors with CVT risk factor like hormonal and genetic factors tend to affect younger age group as compared to arterial stroke risk factor (hypertension, dyslipidemia, diabetes mellitus ex..) who involved older population.

For total patients we did not find a significant seasonal variation in the incidence of CVT, but there was a significant seasonal variation in incidence of CVT in males with higher incidence in summer. There was no similar finding in the few studies that search for seasonal variation for CVT (20-22), Janghorbani et al found an increasing frequency of CVT cases in Autumn season in a study held in Isfahan between 2001-2004, while Ferro et al found a higher incidence in Autumn and winter in a multinational study between 1998 to 2001, Stoltz et al reported a bimodal seasonal variation with higher frequency in Winter and Summer season in a study held in Germany.

We attributed these results to the special climate and social factors in our society as females tend to either work indoors or stay at home (house wives) during hot summer days reducing the environmental effect on their risk of getting CVT, while outdoors job are mostly for males which expose them to higher risk of dehydration and thrombotic events.

Mean incidence rate in the duration between beginning of 2010 to the end of 2019 was 23.97 case per million per year, with lowest incidence rate was 10.64 case per million per year at 2010 and highest was 31 case per-million per year at 2013. This rate tend to be higher than what was reported by Coutinho et al who found incidence rate of 13.2 patients per million per year in Netherland (4), but it was lower than what was found by Daif et al in a study underwent in hospitals of Saudi Arabia at 1995 with incidence of 70 patients per million per year(26). As noticed there is difficulty in estimating incidence in different geographical areas due to different environmental and socioeconomic factors between different nations, with the developing countries has higher incidence rate due to higher fertility rates and higher pregnancy related complications (8).

Study shows a trend of increasing incidence rate with advancing years but this finding was statistically not significant but could show an increase in the awareness toward this rare entity with improving diagnostic tools availability (27), similar results found by Coutinho et al in a met analysis of literatures who reaches a conclusion that there was a trend of improving diagnosis with declining mortality.(9)

Mortality rate for total population in our study was 2.3% which is about the same of what D M Naser et al found on a study including 11400 patients registered in NIS (national inpatient sampl) between

2001 to 2008 with in patients mortality 232 patients (2%).

Study showed no statistical difference in mortality between both genders, this could be explained by the fact that independent risk factors for mortality in CVT was advanced age, sepsis, malignancy and associated autoimmune disease with no gender specific factors.(28) Study showed no significant seasonal variation in mortality rate and this finding was not found in other studies. we could attribute this finding to the fact that mortality in patient with CVT depend on many factors other than environmental and seasonal factors (28).

## CONCLUSION

Cerebral venous thrombosis has higher incidence in females with female male ratio of about 3:1. Cerebral venous thrombosis targeted younger age group than arterial stroke with highest frequency amongst female in reproductive ages with mean age of onset of 33 years with higher incidence in 35-45 years old age group. There was evident seasonal variation with highest incidence of CVT in male gender during summer season, but this finding was absent in total population and female gender. The mean incidence rate during the duration of study was 23.9 patient per million per year. Study found that there was a trend of higher incidence rate toward advanced time of the study although that finding was statistically not significant. Mortality rate of CVT is low. Enhance knowledge and awareness of medical, paramedics and general populations regarding this rare but serious entity and their common clinical presentations and risk factors. Early detection, communication and referral of CVT cases to tertiary centers for better handling and prognosis. Further researches needed to study the clinical aspects and common clinical scenarios in Iraqi patients admitted or attending medical care for diagnosis and treatment of CVT. Common risk factors in our population need to be studied and to determine better way to reduce their deleterious effect. Studies to evaluate best medical approach for managing CVT patients in Iraq need to be conducted. Medical records in our hospitals need to be updated, scientifically organized to include all vital data for all patients. Digital data recording of inpatients and outpatients need to be available for all patients attending medical services.

## Authors' contributions

1; Conceptualization; Data Curation; Investigation; Methodology; Project administration; Resources; Software; Writing – original draft and Writing – review & editing

2; Conceptualization; Data Curation; Investigation; Methodology; Project administration; Writing – original draft and Writing – review & editing

3; Conceptualization; Data Curation; Investigation; Methodology; Project administration; Resources; Writing – original draft and Writing – review & editing

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## Conflicts of interest

The authors declare no conflict of interest regarding this article.

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