DOI: 10.7860/IJNMR/2024/66517.2412

Original Article

Paediatrics Section

Single Umbilical Artery and Associated Systemic Anomalies in Foetal and Perinatal Autopsy: An Observational Study

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ABSTRACT

Introduction: Single Umbilical Artery (SUA) is a congenital anomaly that can occur either as an isolated finding or in association with other systemic anomalies. Several studies have reported that SUA is linked to dysplastic kidneys, ventricular septal defects, oesophageal atresia, spina bifida, diaphragmatic hernia and cystic hygromas. Therefore, investigating cases of SUA in autopsies is crucial.

Aim: To estimate the frequency of SUA in foetal autopsies and determine the association between SUA and other systemic anomalies.

Materials and Methods: The present ambispective observational study was conducted in the Department of Pathology, Shri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Dharwad, Karnataka, India, over a 13 year period from January 2009 to December 2021. A total of 63 cases of SUA detected during foetal autopsies were included. Factors such as age, parity and multiple births were collected where available. The hospital-based frequency of SUA was calculated as a percentage. The association between SUA and systemic anomalies was assessed using the Chi-square test.

Results: A total of 1338 perinatal autopsies were performed during the study period, with SUA present in 63 (4.70%) cases. The most common associated anomaly was genitourinary defects identified in 16 (25.39%) cases. However, a statistically significant association was observed with musculoskeletal (11.11%), nervous (11.11%), and gastrointestinal system anomalies (19.04%) with a p-value of <0.0001.

Conclusion: In the present study, SUA accounted for 4.70% of the foetal autopsies conducted during the study period. The most common associated anomalies were bilateral cystic kidneys, and VATER (Vertebral, Anal, Tracheo-oesophageal, and Renal anomalies) was the most common syndromic associations with SUA.

Keywords: Abortion, Congenital defect, Foetal demise, Umbilical cord, Urogenital abnormalities

INTRODUCTION

Single Umbilical Artery (SUA) is the most common true congenital anomaly of the umbilical cord and was first described by Vesalius [1]. SUA is the most common anomaly of the umbilical cord, accounting for 0.5-6% of all congenital anomalies [2]. When compared with congenital anomalies of all other systems, SUA has a prevalence rate of 1% [3]. Normally, the umbilical cord contains two arteries and one vein. SUA is a condition characterised by the presence of only one umbilical artery. This anomaly is caused by developmental agenesis of one umbilical artery, marked hypoplasia of a previously normally developed umbilical artery, or persistent allantoic artery of the body stalk [4]. The incidence of SUA in twins is three times that of singletons [3]. Previous studies in the literature, depending on the target population being studied, including autopsies, prenatal ultrasonographic examination, or in foetuses born alive or preterm, have reported different rates of SUA detection [4,5]. Studies have reported that compared to radiological and other studies, the incidence of SUA is 3.3 times greater in autopsy series, with an incidence of around 7% [4,5]. SUA is detected either as an isolated finding or it may be associated with other congenital anomalies. Congenital malformations among foetuses with SUA have been reported to be as high as 70% [2,3]. Among the associated systemic anomalies, urological malformations are the most common in foetuses with SUA [3-5]. Various studies have reported that SUA is known to be associated with dysplastic kidneys, ventricular septal defects, oesophageal atresia, spina bifida, diaphragmatic hernia and cystic hygromas [6-10]. Hence, it is important to investigate cases of SUA. Over the years, foetal and perinatal autopsies have drastically reduced in number with no published data in the literature from North Karnataka, India. However, the authors noticed a rising trend in the number of foetal autopsies in our institute over the last decade. This upward trend is mostly attributed to increased awareness among expectant parents consenting to foetal autopsies to determine the cause of death. However, there was a drastic reduction in the number of foetal autopsies during the Coronavirus Disease 2019 (COVID-19) pandemic. As a referral centre and tertiary hospital catering to several districts in North Karnataka, we have undertaken this study to find out the hospital-based frequency of SUA and to carry out a detailed foetal and perinatal autopsy study to look for any other associated systemic anomalies or syndromic associations.

MATERIALS AND METHODS

The present ambispective observational study was conducted at SDM College of Medical Sciences and Hospital, Shri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Dharwad, Karnataka, India, from January 2009 to December 2021. Data encompassed 10 years retrospectively from January 2009 to December 2018, and prospectively for three years from January 2019 to December 2021, after which the entire dataset was analysed. Institutional Ethical Committee clearance was obtained for the study (IEC no: 2022/163).

Inclusion criteria: All SUA cases detected during foetal autopsies within the study period were included.

Exclusion criteria: Autolysed foetuses were excluded from the study.

Study Procedure

For the retrospective study, patient details were gathered from the Digital Medical Record Department of our hospital. Risk factors such as age, parity and multiple births were collected, wherever available. Microscopic slides and gross images were retrieved from the archives in the histopathology section and reviewed. Radiological images (X-ray and ultrasound) were retrieved from the Picture Archiving and Communication System (PACS).

These foetuses were either aborted due to intrauterine death or terminated following the detection of malformations. For prospective cases, detailed foetal autopsies were performed according to Virchow's technique, involving thorough external and internal examinations to detect any associated anomalies [2]. Anthropometry was measured with respect to gestational age and analysed for external anomalies. Externally, the umbilical cord was examined for the number of vessels and any other anomalies. Sections were taken from three different areas of the umbilical cord in each case. Additional sections were taken wherever necessary from abnormal looking sites.

A detailed dissection of the foetus and the autopsy reporting was conducted by senior pathologists. The anatomic relations of each visceral organ, structural abnormalities, and histopathologic examinations were performed. The skull was opened, the brain was removed and examined grossly and histologically. Organs histologically examined included the thymus, lungs, heart, liver, gall bladder, pancreas, spleen, kidneys, testes, uterus, ovaries, brain, and other endocrine organs (adrenals, thyroid, pituitary). X-ray, gross, and microscopic examination of organs with photographic documentation was carried out.

STATISTICAL ANALYSIS

Descriptive measures such as percentages and means were calculated. The hospital-based frequency of SUA was determined as a percentage. The association between SUA and systemic anomalies was calculated using the Chi-square test. A p-value <0.05 was considered statistically significant. Data collected were entered into Microsoft (MS) Excel 2010, and all analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software version 22.0.

RESULTS

A total of 1338 perinatal autopsies were conducted in the present study. Among the 1338 autopsies, various congenital malformations were identified in 356 (26.55%) cases. Out of these 356 foetuses with congenital malformations, SUA was present in 63 (17.69%) cases. Therefore, SUA accounted for a rate of 4.70% among all autopsies performed [Table/Fig-1].

Out of the 63 foetuses, 39 (61.91%) were males, while 24 (38.09%) were females, resulting in a male to female ratio of 1.6:1. The mean maternal age was 24.75 years (range 19-35 years), with the majority, n=51 (80.95%) falling between the ages of 20-30 years. There were 27 (42.86%) primigravidae, and in 36 (57.14%) of cases, maternal gravida status was Gravida 2 (G2) and above. The mean gestational age at the time of diagnosis was 26.33 weeks (range 8-39 weeks). History of consanguinity was present in 1 (1.58%) case. Two cases of multiple pregnancies with SUA were identified, with the anomaly observed in the smaller twin [Table/Fig-2].

Year	Total no. of autopsies performed, n	Total no. of congenital malformations, n	Total no. of SUA cases, n	Total no. of SUA cases with congenital malformation, n
2009	60	18	02	2
2010	72	22	03	1
2011	68	16	05	1
2012	105	16	08	7
2013	85	15	00	0
2014	155	28	02	2
2015	180	40	03	1
2016	167	56	09	8
2017	135	63	15	10
2018	165	36	04	2
2019	96	34	10	4
2020	28	05	01	0
2021	22	07	01	1
Total, n (%)	N=1338	356 (26.55)	63 (4.70)	39 (61.90)

[Table/Fig-1]: Annual data depicting the total number of autopsies performed, total number of cases with congenital malformations and number of cases with SUA.

Foetal and maternal factors	Number (n)	Percentage (%)
Gender of stillborn foetuses		
Male	39	61.91
Female	24	38.09
Twins		
Present	1	1.59
Absent	62	98.41
Gravida		
Primi	27	42.86
G2 and above	36	57.14
Maternal age (years)		
<20	3	4.76
20-30	51	80.95
>30	9	14.28
Maternal age (years)	Mean: 24.75	Range: 19-35
Gestational age (weeks)	26.33	8-39

[Table/Fig-2]: Descriptive statistics of foetal and maternal factors in the present study (n=63).

Systemic anomalies were associated with 39 (61.90%) cases. Among these cases, 24 were males and 15 were females, with a male to female ratio of 1.6:1. While some cases had systemic involvement limited to a single organ, many cases of SUA exhibited involvement of multiple systems [Table/Fig-3]. Ultrasonography was performed for all cases, with 40 (63.49%) resulting in intrauterine death and 23 (36.50%) in terminated pregnancies.

The most common systemic anomaly associated with SUA was bilateral dysplastic kidneys in the genitourinary system, followed by unilateral renal agenesis. The gastrointestinal system showed imperforate anus as the most common anomaly. Other systemic anomalies included Tetralogy of Fallot (TOF), atrial septal defect, and vertebral anomalies [Table/Fig-4].

In the present study, 53 (84.1%) cases of SUA showed no other findings in the umbilical cord. However, in the remaining 10 cases, findings in the umbilical cord included UC torsion (1 case), furcated

System involved by congenital anomalies	Anomalous cases without SUA (n=356), n (%)	Anomalous cases with SUA (n=39), n (%)
Nervous system	143 (40.16)	7 (11.11)
Genitourinary system	71 (19.94)	16 (25.39)
Cardiovascular system	52 (14.60)	9 (14.28)
Gastrointestinal system	32 (8.98)	12 (19.04)
Foetal hydrops	24 (6.74)	2 (3.17)
Musculoskeletal system	20 (5.61)	7 (11.11)
Respiratory system	14 (3.93)	2 (3.17)

[Table/Fig-3]: Showing system-wise distribution of congenital anomalies. A statistically significant association was observed with musculoskeletal, nervous and gastrointestinal system anomalies (p-value<0.0001)

System involved	Associated systemic anomalies	n
Genitourinary system	Bilateral dysplastic kidneys	8
	Unilateral renal agenesis	5
	Horse-shoe kidney	1
	Glomerular cystic disease	1
	Common cloaca	1
Gastrointestinal system	Imperforate anus	5
	Oesophageal atresia	2
	Diaphragmatic hernia	3
	Omphalocele	1
	Meckel's diverticulum	1
Cardiovascular system	TOF	2
	ASD	2
	VSD	1
	Single atrium	1
	TGV	1
	Situs inversus totalis	1
	Right ventricular hypoplasia	1
Musculoskeletal system	Vertebral anomalies	3
	Absent toes/fingers	1
	Bilateral club foot	1
	Sirenomelia	1
	Micrognathia	1
Central nervous system	Neural tube defects	6
	a. Encephalocele	3
	b. Exencephaly	1
	c. Iniencephaly	1
	d. Spina bifida	1
	Hydrocephalus	1
Respiratory system	Pulmonary hypoplasia	2
Hydrops	-	2

[Table/Fig-4]: Depicting the specific systemic anomalies in association with SUA.
ASD: Atrial septal defect; VSD: Ventricular septal defect; TGV: Transposition of great vessels; TOF: Tetralogy of fallot

insertion (1 case), UC artery and vein thrombosis (2 cases), cord around the neck (1 case), true knot of the umbilical cord (2 cases), and UC flattening (1 case). Microscopic examination of one umbilical cord revealed squamous metaplasia of the lining epithelium (1 case) and oedematous and dilated UC vein (1 case) [Table/Fig-5].

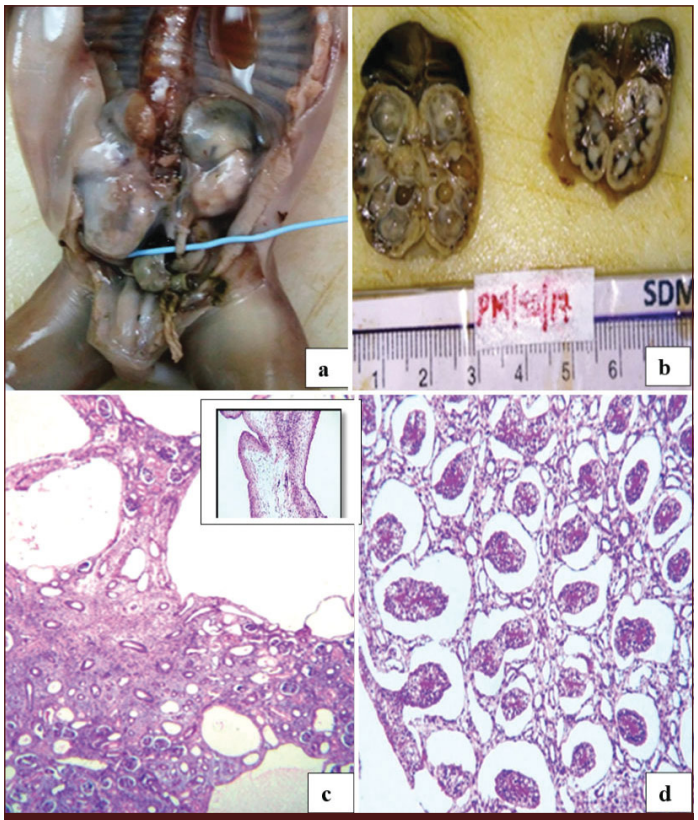
Six cases showed syndromic associations. Among these, three cases were associated with VATER anomaly, while one case each was linked to VACTERL (Vertebral Defects, Anal Atresia, Cardiac Defects, Tracheo-esophageal Fistula, Renal Anomalies, and Limb Abnormalities) anomaly, DiGeorge syndrome, and iniencephaly sequence [Table/Fig-6,7a-d,8a-d,9a-f].

Umbilical cord findings	n (%)
SUA only	53 (84.12)
SUA with UC torsion	1 (1.58)
SUA with furcated insertion	1 (1.58)
SUA with UC artery and vein thrombosis	2 (3.17)
SUA with true knot	2 (3.17)
SUA with UC flattening	1 (1.58)
SUA with squamous metaplasia of lining epithelium	1 (1.58)
SUA with cord around neck	1 (1.58)
SUA with oedematous and dilated UC vein	1 (1.58)

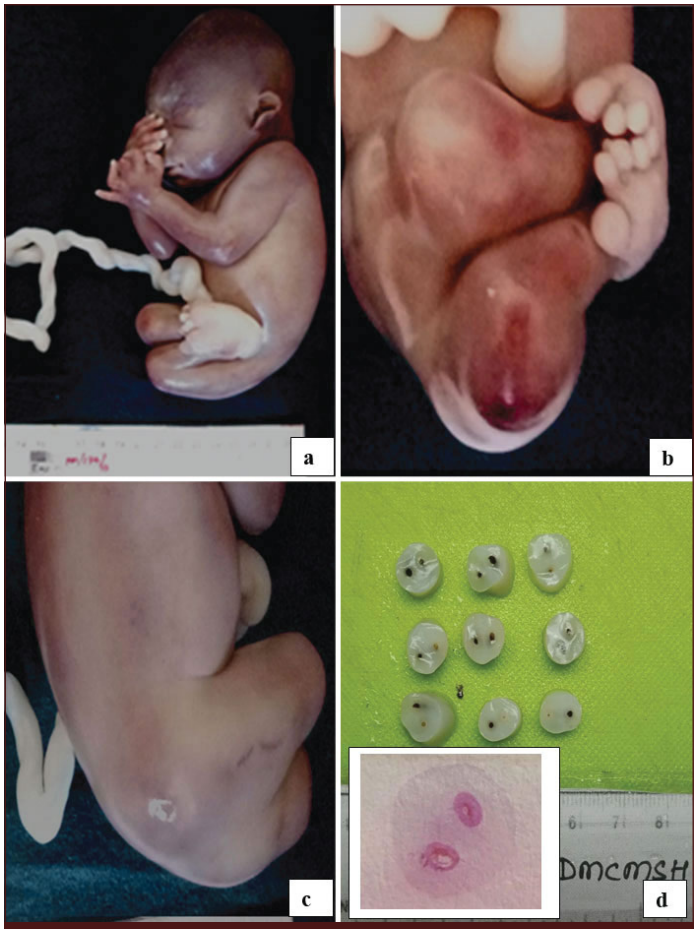
[Table/Fig-5]: Depicting gross and microscopic findings in the Umbilical Cord (UC) in SUA cases.

Systemic anomalies	Syndromes
Imperforate anus, SUA, absent thymus, TOF (with LVH), cystic dysplasia of kidneys. X-ray: Kyphoscoliosis. Microscopy: Cystic dysplasia of kidneys	DiGeorge syndrome
Bilateral cystic renal dysplasia with limb defect and SUA	VACTERL
Low set ears, micrognathia, receeding chin, imperforate anus, tracheo-esophageal fistula, Rectum opens into prostatic urethra	VATER
Cervicothoracic encephalocele, imperforate anus, dysplastic bilateral kidneys, multiple vertebral anomalies	VATER
Imperforate anus, multicystic dysplasia of left kidney, absent right kidney	VATER
Iniencephaly apertus, diaphragmatic hernia, spina bifida, encephalocele, asplenia, pulmonary hypoplasia, arthrogryposis, low set ears	Iniencephaly sequence

[Table/Fig-6]: Showing the various syndromes associated with SUA.



[Table/Fig-7]: Case of SUA with multicystic renal dysplasia and glomerulocystic disease: Autopsy of 20 weeks foetus showing: a) Enlarged right pelvic kidney; b) Cut section of the enlarged right kidney showing multiple cysts; c) Microscopy of right pelvic kidney showing features of dysplastic kidney (inset) (H&E, 10x); d) Microscopy of left kidney showing features of glomerulocystic disease (H&E, 40x).



[Table/Fig-8]: Sirenomilia: a-c) 20 weeks foetus with fused lower limbs, short neck, low set ears and finger deformity with imperforate anus; d) Gross and microscopy (Inset) of umbilicus showing Single Umbilical Artery (SUA).

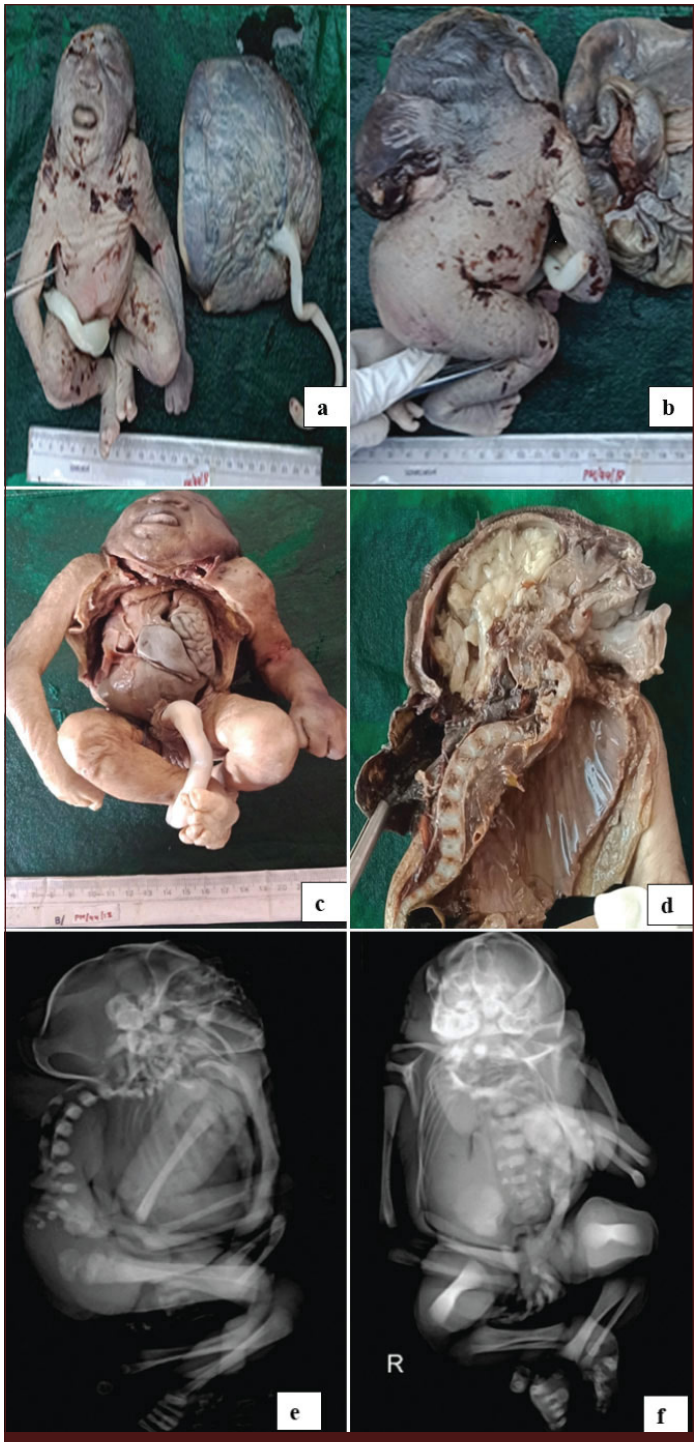
DISCUSSION

Congenital anomalies contribute significantly to foetal, perinatal, and infant mortality globally, and they are the leading cause of infant mortality in developed countries. However, developing countries like India are still facing challenges such as low birth weight, prematurity and sepsis, which are major causes of infant mortality. Due to these challenges, not much attention has been given to the burden of congenital malformations in India, despite being the fifth most common cause of infant mortality. They account for 8-15% of perinatal deaths in India [7].

Antenatal investigations play a crucial role in diagnosing congenital malformations. Ultrasonography remains the preferred imaging modality as it is non invasive, safe, cost-effective and sensitive. The introduction of new techniques like first trimester endovaginal sonography and three-dimensional imaging has significantly improved the diagnostic accuracy of congenital malformations. In addition to routine investigations, procedures such as ultrasound-guided amniocentesis, quadruple screen tests Alpha-Fetoprotein (AFP) immunoassay, and genetic studies like Deoxyribonucleic Acid (DNA) microarray are useful for early prenatal detection of congenital malformations [8].

Although ultrasonography provides fairly accurate diagnosis, examining terminated foetuses is essential for confirming the diagnosis and identifying any other associated anomalies that may have been missed or are undetectable on ultrasound. Therefore, perinatal autopsy remains the gold standard procedure for terminated and aborted foetuses [9].

In the present study, out of 1338 autopsies performed, congenital malformations were found in 356 (26.55%) cases. A literature review



[Table/Fig-9]: SUA with iniencephaly apertus: a): A 20 weeks foetus with typical stargazing appearance with short /absent neck, open mouth with large protruding tongue and low set ears; b): Marked lordosis, short neck and large encephalocele in occipital region; c): Diaphragmatic hernia; d): Sagittal section showing abnormal fusion of deformed cervical vertebrae and defect in the occipital bone with large occipital sac (encephalocele); e) and f): Foetal X-ray displaying absence of cervico-thoracic regions of vertebral column, defective fusion of vertebral arches, lumbar kyphosis, retroflexed head on the cervical spine and fixed flexion of the body.

revealed that similar studies conducted by Padma S et al., Rittler M et al., and Kambala MG et al., reported 27%, 30.9% and 36.7% of congenital malformations, respectively [9-11].

In the present study, the most common congenital defect encountered was of the Central Nervous System (CNS), observed in 133 (37.46%) cases. A similar predominance of CNS anomalies was reported by Kambala GM et al., (33.3%) and Swain AA and Bhatia BD (39.5%) [11,12]. However, Rittler M et al., reported hydrops (22.88%) as the most common congenital malformation [10]. The third most common congenital anomaly observed in the present

study was SUA. However, Rittler M et al., in their study reported SUA as the seventh and least common congenital anomaly [10].

Pathological lesions occurring in the umbilicus may or may not have clinical significance. Lesions such as remnants of the allantoic duct and omphalomesenteric duct are incidental findings without much pathological significance [2].

The development of umbilical cord elements takes place between 13 days and 38 days of conception. Although the etiopathogenesis of SUA is not entirely clear, it is hypothesised that it could be due to: (a) Aplasia or atrophy of one umbilical artery; (b) Secondary atresia or atrophy of a previously normal umbilical artery; (c) An abnormal vitelline origin of a single artery in the body stalk of the embryo [4,10,13]. Studies have reported a low incidence of SUA in very early embryos, strongly suggesting that secondary atrophy or atresia could be the mechanism responsible for the majority of SUA cases [4,10,14].

A male predilection was reported in a previous study [14]. Another study found that malformations with SUA are more commonly seen in male foetuses [15]. A similar observation was noted in the present study, with a male-to-female ratio in SUA with associated malformations being 1.6:1.

The reported incidence of SUA in twin pregnancies is 5-11%, with a 3-7 fold increased risk of SUA compared with singletons [14]. It has also been observed that SUA is almost always seen in the smaller twin [1]. The present study included two twin pregnancies, and SUA was observed in the smaller twin.

The rate of SUA in the current study was 4.70%, which was similar to that reported by Anita AM et al., (3.10%) and Rittler M et al., (2.4%) [10,15]. However, higher rates (7.9%) were reported by Abuhamad AZ et al., which may be due to a smaller sample size [5]. Rittler M et al., reported SUA as the 7th most common congenital malformation among all other systems, accounting for 2.4% [10]. In the current study, SUA was the third most common congenital anomaly, accounting for 17.69% of the autopsies, with isolated SUA in 4.70% of cases. SUA may be associated with other systemic anomalies or occur as an isolated defect [16]. In the present study, out of 63 cases, associated systemic anomalies were noted in 39 (61.90%) cases. Out of the 39 cases, there were 24 male foetuses and 15 female foetuses, with a male-to-female ratio of 1.6:1. In some cases, systemic involvement was restricted to only one organ, but many cases of SUA had multiple system involvement. Several studies have shown that associated anomalies in cases of SUA ranged between 14% to 65%, and among the systems involved, renal anomalies were more commonly associated [1,10].

In the present study, 61.90% of SUA cases involved other systemic malformations. A similar incidence was reported by Anita AM et al., (80%), Heifetz SA (81%) and Rittler M et al., (83%) [10,15,17]. However, a study by Froehlich LA and Fujikura T reported a relatively lower associated incidence of 53%, probably due to methodological differences [18]. Many studies have reported a significant association between SUA and urinary tract defects [10,15]. In the present study, genitourinary defects were more commonly involved and accounted for 16 (25.39%) cases. Similar findings were reported by Rittler M et al., (36.3%) and Anita AM et al., (60%) [10,15]. The present study showed that 19.04% of cases with SUA had gastrointestinal anomalies. Gastrointestinal tract anomalies were the second most common system involved in the present study, with a significant association in accordance with Rittler M et al., who reported CVS as the second most common system involved followed by Gastrointestinal Tract (GIT) [10]. The present study showed that 14.28% of cases with SUA had a cardiovascular anomaly of varying degrees of severity, which included TOF, atrial septal defect, ventricular septal defect, single atrium, transposition of great vessels, situs inversus totalis and right ventricular hypoplasia. Rittler M et al., reported 21.5% of cases with CVS anomalies having SUA [10]. The present study showed that 11.11% of cases with SUA had nervous system anomalies. Similar findings were reported by Rittler M et al., amounting to 16.3% of cases [10]. In our study, it showed a significant association with the majority of cases involving neural tube defects followed by hydrocephalus. The present study showed that 11.11% of cases with SUA had musculoskeletal system anomalies, similar to a study conducted by Froehlich LA and Fujikura T amounting to 13% [18].

Comparison with several similar studies over the past few years shows varying rates of SUA among the foetal autopsies performed, ranging from 2.4% to 11.11%, depending on the sample size and the duration of the study [3,10,15,19,20]. In the present study, the rate of SUA was 4.70% [Table/Fig-10]. Although several studies in the literature worldwide have studied the incidence of SUA and its systemic associations, none of them have discussed in detail the syndromic associations, which was an existing knowledge gap [Table/Fig-10] [3,10,15,19,20]. The strength and novelty of the current study are that to date, the association between SUA and syndromes has not been reported in detail in the literature. Hence, the authors have made an attempt to study the syndromic association with SUA, which was seen in six cases in the present study. Of the six cases, three cases showed an association between SUA and VATER anomaly, and one case each with VACTERL anomaly, DiGeorge syndrome and iniencephaly sequence. A 20-week foetus with classical features of sirenomelia characterised by fused lower limbs, short neck, low-set ears, finger deformity and imperforate anus was also noted [Table/Fig-8]. Iniencephaly is a rare neural tube defect characterised by extreme retroflexion of the head with the absence of the neck due to spinal deformities. Fusion of malformed cervical and thoracic vertebrae is also noted with an upward-turned face due to the absence of the neck, giving a stargazing

Author of the study	Place of the study	Study period (in years)	No. of autopsies	No. of cases with congenital malformation, n (%), n	No. of cases with SUA, n (%), n	Incidence of SUA
Rittler M et al., [10]	Argentina	1980-2005 (25 years)	5539	1713 (30.9)	135 (7.88)	2.4%
Anita AM et al., [15]	Kalburgi, India	2016-2017 (1.5 years)	322	59 (18.32)	10 (16.94)	3.10%
Nayak SS et al., [3]	Manipal, India	5 years	214	--	17	7.9%
Huria A and Kochhar S [19]	Chandigarh, India	January 2010-November 2011 (2 years)	150	104	5	3%
Mounika P et al., [20]	Telangana, India	January 2013-July 2021 (9 years)	81	-	9	11.11%
Present study	Dharwad, India	2009-2021 (13 years)	1338	356 (26.55)	63 (17.69)	4.70%

[Table/Fig-10]: Comparison of other similar studies with respect to rate of SUA among total number of autopsies [3,10,15,19,20].

appearance. Many case reports in the literature have published the classic radiological findings of iniencephaly. However, there are just a few case reports describing the necropsy findings of this condition [21]. In the current study, the foetal X-ray revealed a defect in the occipital bone with occipital encephalocele, non visualisation of cervical and thoracic vertebrae, thoracic lordosis, lumbar kyphosis and fixed flexion of the body [Table/Fig-9].

Limitation(s)

Some limitations in the present study included the lack of cytogenetic testing. Since it was predominantly a retrospective study, some clinical details were missing in a few cases, and the authors had to rely solely on the data available from case records.

CONCLUSION(S)

In the present study, SUA accounted for 4.70% of the foetal autopsies performed during the study period. Systemic malformations were noted in 61.9% of SUA cases. The most common associated anomalies were bilateral cystic kidneys and neural tube defects, including encephalocele, iniencephaly and spina bifida. VATER was the most common syndromic association with SUA. The present study also highlights the importance of foetal autopsy and recommends that foetal autopsy should be performed in all stillbirths and intrauterine foetal demises, even when prenatal sonography has detected any congenital anomalies, and also provides an opportunity for genetic studies, wherever facilities are available. Hence, foetal autopsy still remains the gold standard procedure to confirm the already detected anomalies and to identify any additional abnormalities.

Acknowledgement

The authors express their sincere gratitude to the Department of Obstetrics and Gynecology for their support and encouragement. Also, the authors would like to thank the laboratory technicians for their skilled technical assistance.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 15, 2023
- Manual Googling: Nov 21, 2023
- iThenticate Software: Jan 22, 2024 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jul 15, 2023**
Date of Peer Review: **Sep 12, 2023**
Date of Acceptance: **Jan 24, 2024**
Date of Publishing: **Jun 30, 2024**