

# Metabolic Syndrome in Childhood Cancer Survivors: Does Delta BMI Predict Risk in Lower-middle-income Countries?

**Arushi Agarwal**

Rajiv Gandhi Cancer Institute and Research Centre

**Gauri Kapoor** (✉ [kapoor.gauri@rgcirc.org](mailto:kapoor.gauri@rgcirc.org))

Rajiv Gandhi Cancer Institute and Research Centre <https://orcid.org/0000-0002-0720-8336>

**Sandeep Jain**

Rajiv Gandhi Cancer Institute and Research Centre

**Payal Malhotra**

Rajiv Gandhi Cancer Institute and Research Centre

**Anurag Sharma**

Rajiv Gandhi Cancer Institute and Research Centre

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## Research Article

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# Abstract

**Purpose** Metabolic syndrome (MetSyn) is an important late effect of childhood cancer. The combination of rising obesity and high prevalence of under-nutrition at diagnosis, make this a unique population to study in LMIC (lower middle-income countries).

**Methods** Children  $\leq 18$  years of age at cancer diagnosis, in a single-centre in a LMIC, who were disease free and had completed treatment at least 2 years prior to study were included. MetSyn was defined using International Federation for Diabetes criteria for Asian Indians. Logistic regression analyses were carried out to evaluate the influence of various risk factors, including delta BMI (increase in body mass index from diagnosis to evaluation), on MetSyn.

**Results** A high prevalence of MetSyn (12.2%), central obesity (33%), and dyslipidemia (61.8%) was found in a cohort of 500 Asian Indian childhood cancer survivors (CCS) at a median follow-up age of 17 years. Multivariable analysis revealed older age at diagnosis  $\geq 10$  years, OR 2.9(1.6-5), longer survival duration  $\geq 10$  years, OR 2.2(1.3-3.8), high BMI at diagnosis OR 3.2(1.5-6.9) and large delta BMI  $\geq 50$ , OR 3.15(1.7-5.9) to be independent predictors of MetSyn. Patients who were under-weight or normal at diagnosis with large Delta BMI  $\geq 50$  had very high odds (OR, 12.5,1.7-92) of developing MetSyn compared to those with lower Delta BMI.

**Conclusions and implications for cancer survivors:** A high prevalence of MetSyn was observed in CCS with early age at onset. Timely screening and early intervention are proven to be beneficial and delta BMI could be a useful screening tool for LMIC.

## Introduction

With improved survival of childhood cancers, late effects have emerged as a serious area of concern. As a result, survivors of childhood cancer are at an increased risk of chronic health conditions such as cardio-metabolic disorders, pulmonary problems, stroke, diabetes and second neoplasms. This is true even in the lower middle-income countries (LMIC) as evidenced by an ever-increasing number of survivors, particularly in Asian Indians [1-3]. Of concern is the substantially elevated risk of cardiovascular diseases (CVD) observed in numerous investigations worldwide [4-8] and Oeffinger et al observed this risk to be 10 times higher in childhood cancer survivors (CCS) in the US as compared to their siblings [8]. Metabolic syndrome (MetSyn) is an important predictor of CVD and constitutes a cluster of risk factors including obesity, glucose intolerance, insulin resistance, dyslipidemia, and hypertension [9]. Although the epidemiology of MetSyn is multifactorial, it is to a large extent determined by modifiable factors like obesity, dietary habits and sedentary life style.

Recent data shows that obesity, is rising in every region of the world, and may in fact be increasing more rapidly in the LMIC than in the high-income countries (HIC) [10-12]. Furthermore, the majority of undernourished children live in LMIC [13]. Hence, child under-nutrition and adult obesity coexist in many LMIC (e.g., India), leading to sarcopenic obesity wherein deficits of muscle mass relative to fat persist into

adulthood. This dual combination has been implicated as a risk factor for cardio-metabolic disorders unique to LMIC [14-17]. Recent studies indicate that even among those who are not overweight or obese, the increase in BMI (delta) during growth and development should be closely monitored, as it may predict early onset MetSyn [18]. Hence, we planned to study delta BMI in this context as it has not previously been evaluated among CCS. The present study aims to address this knowledge deficit by analyzing the prevalence of MetSyn in CCS in a LMIC setting and determine the risk factors associated with it.

## Methods

### *Patient selection*

This was a cross-sectional, observational, single-centre study, conducted over a period of 18 months, from July 2018 to December 2019, in a tertiary care cancer centre. The Pediatric Oncology department of our Institute runs an after completion of therapy (ACT) clinic, where all off-therapy patients are registered. The hospital and ACT e-database were mined to identify CCS who were  $\leq 18$  years at diagnosis, in complete remission and at least two years from treatment completion. Among 1430 patients registered in the hospital, data for 954 patients was available in the ACT e-database, of these 714 could be contacted telephonically; 500 consented and were evaluated at the ACT clinic. The evaluation comprised a complete history (including details of anti-hypertensive and anti-hyperglycemic medication), physical examination, anthropometry, and laboratory tests. Demographic, socioeconomic, disease and treatment details were extracted from the e-medical records. Exposure to various classes of chemotherapeutic agents (anthracycline, alkylating agent, anti-metabolite), steroids and cumulative equivalence doses of anthracycline were calculated. Radiation fields and doses were obtained and categorized as cranial, head and neck (not brain), chest, abdomen/pelvis, extremity and other). Assessment of urban/ rural residence and socioeconomic class was done based on the Kuppuswamy scale (based on overall family income, occupation and education) [19]. The study received approval from the Institute's ethics committee and written informed consent was obtained from patients/parents (for minors).

BMI was calculated as:  $BMI = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$ . Nutritional status was defined as per Centre for Disease Control (CDC) and WHO criteria using Asia-Pacific guidelines for South Asians: age 5-19 years, BMI  $< 5^{\text{th}}$  percentile was defined as underweight, BMI =  $5^{\text{th}}$  to  $< 85^{\text{th}}$  percentile defined as normally nourished, BMI  $\geq 85^{\text{th}}$  to  $< 95^{\text{th}}$  percentile as overweight and  $\geq 95^{\text{th}}$  percentile as obese, adjusted for age and sex; age  $> 19$  years, BMI  $< 18.5 \text{ kg/m}^2$  were defined as underweight, normal BMI range was  $18.5\text{-}22.9 \text{ kg/m}^2$ , BMI  $\geq 23 \text{ kg/m}^2$  to  $< 25 \text{ kg/m}^2$  was defined as overweight and those with BMI  $\geq 25 \text{ kg/m}^2$  as obese [20, 21]. Delta BMI was calculated as the percentage change in BMI z-score from diagnosis to follow-up evaluation.  $\text{Delta BMI} = [(\text{BMI z-score at evaluation} - \text{BMI z-score at diagnosis}) / \text{BMI z-score at diagnosis}] \times 100$ . Waist circumference (WC) was measured midway between the lowest rib and the top of the iliac crest at the end of expiration in a standing position using a fiberglass tape with an accuracy of 1 mm. For survivors  $< 18$  years of age at evaluation, age- and sex-specific reference percentiles for WC reported in Indian children by Khadilkar et al. were utilized as normative data for defining central obesity [22].

International Diabetes Federation (IDF) criteria for Asian Indians were utilized for adults [23]. Blood pressure (BP) was measured in the right upper arm in sitting position using mercury sphygmomanometer with an appropriate size cuff. Hypertension (HT) was defined as systolic or diastolic values  $\geq 90^{\text{th}}$  percentile for age, sex, and height. Blood biochemistries included fasting blood glucose (FBG) and lipid profile after 12 hours of overnight fasting.

## ***Definition of MetSyn***

Using IDF criteria cut-offs for Asian Indians, MetSyn was defined [23] as follows for children 10 to 15 years of age as having central obesity ( $WC \geq 90^{\text{th}}$  percentile) plus two or more of the following criteria: (1) Triglycerides (TGs)  $\geq 150$  mg/dL, (2) High-density lipoprotein cholesterol (HDL-c)  $< 40$  mg/dL, (3) systolic BP (SBP)  $\geq 130$  mm Hg or diastolic BP (DBP)  $\geq 85$  mm Hg, (4) FBG  $\geq 100$  mg/dL. For those  $\geq 16$  years of age, MetSyn was defined as having central obesity ( $WC \geq 90$  cm for men and  $\geq 80$  cm for women), plus 2 or more of the following criteria: (1) TGs  $\geq 150$  mg/dL, (2) HDL-c  $< 40$  mg/dL in males and  $< 50$  mg/dL in females, (3) SBP  $\geq 130$  mm Hg or DBP  $\geq 85$  mm Hg, (4) FBG  $\geq 100$  mg/dL. As per IDF guidelines children 6 to  $< 10$  years of age were identified as high risk if their  $WC \geq 90^{\text{th}}$  percentile and had a family history; in which case further measurements were carried out [24].

## ***Statistical analysis***

The participants' demographic, disease and treatment details were analysed by descriptive statistics and mean ( $\pm$  standard deviation, SD) or median (inter quartile range, IQR) were used as appropriate. Fischer's exact test and chi-square test were utilized for categorical variables. Quantitative variables were compared using the Student t-test or the Mann-Whitney test. Analysis of variance (ANOVA) was used to compare delta BMI among various nutrition categories (underweight and normal versus overweight and obese). Logistic regression analysis was done to investigate the influence of various pre-treatment and treatment related factors on MetSyn among the survivors. Adjusted OR was calculated to study the impact these factors on individual components of MetSyn. Factors with p value  $< 0.05$  on univariate analysis were included for multivariable analysis. A receiver operating characteristic (ROC) curve was plotted to determine the cut-off value of delta BMI to predict MetSyn. The results were interpreted using odds ratio (OR) and 95% confidence interval (CI), and the significance threshold was set as p-value of  $< 0.05$ . Statistical analysis was performed using the SPSS software (version 23.0, 2011; IBM, Armonk, NY, USA).

## **Results**

Five hundred CCS were enrolled in the present study; 78% (389) were male, 85% (424) belonged to the middle class and 74% (370) were from urban areas. At the time of evaluation, the median age of the

survivors was 17 years, 49% (245) were adults  $\geq 18$  years of age, median survival duration was 7 years and 32.6% (163) had survived for  $\geq 10$  years. Based on BMI at diagnosis, the patients were categorized as underweight (130, 26%), normal (295, 59%), overweight (36, 7.2%) and obese (39, 7.8%). The two most common primary diagnoses were acute lymphoblastic leukemia (ALL) (226, 45.2%) and Hodgkin lymphoma (82, 16.4%). Treatment exposures included chemotherapy in all, steroids in 53% (265), radiotherapy (RT) in 32.4% (162), definitive surgery in 23.4% (117) and bone marrow transplant (BMT) in 2.8% (14) of patients (Table 1).

### **Table 1**

Characteristics of childhood cancer survivors with and without metabolic syndrome (MetSyn)

Characteristics	No MetSyn N=439(%)	MetSyn N=61(%)	P value
Sex			0.031
Male	335 (76.3)	54 (88.5)	
Female	104 (23.7)	7 (11.5)	
Median age at diagnosis (years)	8 (IQR:4-12)	11 (IQR:6-15)	0.003
Age at diagnosis			
<10 years	278 (63.3)	23 (37.7)	<0.001
10-18 years	161 (36.7)	38 (62.3)	
Median age at evaluation (years)	17 (IQR:12-21)	22 (IQR:6-15)	<0.001
<18 years	240 (54.7)	15 (24.6)	<0.001
≥ 18 years	199 (45.3)	46 (75.4)	
Median duration from treatment completion (years)	6.7±3.6	9.2±4.8	<0.001
Survival time from diagnosis			
< 10 years	306 (69.7)	31 (50.8)	0.005
≥ 10 years	133 (30.3)	30 (49.2)	
BMI at diagnosis			
Underweight, normal	385 (87.7)	40 (65.6)	<0.001
Obese, overweight	54 (12.4)	21 (34.4)	
Delta BMI			
≥50	48 (10.9)	17 (27.9)	0.008

<50	391 (89.1)	44 (72.1)	
<b>Primary diagnosis</b>			
Hematological malignancy	319 (72.7)	48 (78.7)	0.357
Solid tumor & brain tumor	120 (27.3)	13 (21.3)	
Hematological malignancy			
Acute lymphoblastic leukemia	198 (45.5)	28 (43.1)	0.906
Acute myeloid leukemia	17 (3.9)	3 (4.6)	0.696
Non-hodgkin lymphoma	35 (8)	4 (6.2)	0.699
Hodgkin lymphoma	69 (15.9)	13 (20)	0.269
Solid tumor			
Osteosarcoma/ Ewing sarcoma	51 (11.7)	6 (9.2)	0.681
Rhabdomyosarcoma	23 (5.3)	0 (0)	0.06
Wilms tumor	15 (3.4)	3 (4.6)	0.555
Neuroblastoma	7 (1.6)	0 (0)	0.32
Germ cell tumor	17 (3.9)	3 (4.6)	0.696
Others	3 (0.7)	0 (0)	0.517
Brain tumor	4 (0.9)	1 (1.5)	0.592
<b>Treatment Exposure</b>			
Chemotherapy			
Alkylating	405 (92.25)	58 (95.1)	0.429
Antimetabolite	271 (61.7)	37 (60.65)	0.871
Steroid			
Yes	233 (10.9)	32 (27.9)	0.928
No	206 (89.1)	29 (72.1)	
Radiotherapy			
Brain	68 (15.6)	14	0.14

		(21.5)	
Head & neck not brain	24 (5.5)	4 (6.2)	0.728
Abdomen & pelvis	21 (4.8)	1 (1.5)	0.261
Chest	10 (2.3)	3 (4.6)	0.224
Extremity	4 (0.9)	3 (4.6)	<b>0.012</b>
Others	9 (2.1)	1 (1.5)	0.829
Surgery	107 (24.4)	10 (16.4)	0.1713
Bone marrow transplant	12 (2.7)	2 (3.3)	0.8092
IQR, interquartile range; BMI, body mass index. Delta BMI is percent change in BMI z-score from diagnosis to evaluation.			

## ***Prevalence of MetSyn and its components***

The prevalence of MetSyn in the CCS was 12.2% (61) at a median age of 22 years, their characteristics are detailed in categorical Table 1. The prevalence was lower in children/ adolescents (<18 years, 6%) and higher in adults  $\geq 18$  years (19%). Figure 1 clearly demonstrates the age-wise increment in both males and females. Among the children 6-10 years of age, 28.5% (13/49) were obese by BMI and 22.4% (11/49) had central obesity (WC > 90th centile). Those with family history for cardiovascular risk factors were further assessed and 3 (all were male) of these survivors were observed to have HT (> 90th centile for age and height), elevated TG (>150 mg/dL) and low HDL-c (< 40 mg/dL), hence for the purpose of this analysis they were considered to have MetSyn.

Derangements in individual components [central obesity, impaired fasting glycemia (IFG), hypertriglyceridemia (high TG), low HDL-c, HT] of MetSyn were observed in 68.6% (343) of CCS, one component was abnormal in 40.2% (201) and two components in 16.2% (81). Low values for HDL-c and high WC (central obesity) were the most frequently observed derangements (Table 2). Their frequency and mean values were significantly higher among survivors with MetSyn and in those with high delta BMI (Table 2). It is noteworthy that, 40/61 survivors who developed MetSyn were non-obese/overweight at diagnosis.

**Table 2**

Prevalence of components of metabolic syndrome (MetSyn) and their mean values among childhood cancer survivors by presence of MetSyn and delta body mass index (BMI)

Components of MetSyn	No MetSyn N=439(%)	MetSyn N=61(%)	P- value	Delta BMI	Delta BMI	P- value
				<50 N=435 (%)	≥50 N=65 (%)	
<b>Prevalence of individual components</b>						
Central obesity (WC)	104 (23.7)	61 (100)	<0.001	87 (20.0)	40 (61.5)	<0.001
Hypertriglyceridemia	19 (4.3)	29 (47.5)	<0.001	36 (8.3)	12 (18.5)	0.021
Low HDL-c	242 (55.1)	55 (90.2)	<0.001	250 (57.5)	47 (72.3)	0.030
IFG	8 (1.8)	13 (21.3)	0.002	13 (3.0)	8 (12.3)	0.003
Hypertension	23 (5.2)	39 (63.9)	<0.001	50 (11.5)	12 (18.5)	0.153
<b>Mean values</b>	<b>Mean±SD</b>	<b>Mean±SD</b>		<b>Mean±SD</b>	<b>Mean±SD</b>	
WC	75.1±12.8	96.7±8.0	<0.001	76.2±13.9	92.1±8.7	<0.001
TG	77.3±36.6	132.6±65.6	<0.001	81.2±41.8	103.1±59	<0.001
HDL-c	40.1±9.1	34.9±6.2	<0.001	39.9±9.1	36.5±7.7	<0.001
FBG	83.8±7.0	94.8±26.2	0.002	84.5±8	89.4±24.9	<0.001
SBP	108.2±13.1	126.5±12	<0.001	109.8±13.4	116.5±11.7	<0.001
DBP	67±9.4	78.3±9	<0.001	68±9.6	72±8.4	<0.001
<b>No of components</b>						
0	157 (35.8)	0 (0)	<0.001	154 (35.4)	4 (6.2)	<0.001
1	201(45.8)	0 (0)	<0.001	180 (41.4)	21 (32.3)	0.18
2	81 (18.5)	0 (0)	<0.001	58 (13.3)	26 (40)	<0.001
≥3	0 (0)	61 (100)	<0.001	43 (9.9)	14 (21.5)	<0.001
SD, standard deviation; WC, Waist circumference; IFG, Impaired fasting glycemia; TG, Triglycerides; HDL-c, High-density lipoprotein cholesterol; FBG, fasting blood glucose; SBP, Systolic Blood Pressure; DBP; Diastolic Blood Pressure.						

## ***Delta BMI and Nutritional status***

Calculation of means and SD of percent BMI z-score increment from diagnosis to evaluation (delta BMI) revealed that the highest delta BMI occurred among those who were underweight (74±2) and normally nourished (123±53) at diagnosis, followed by those who were obese (15.8±1.4) and overweight (7.9±1.5), p, 0.04 (Supplemental Table 1). The ROC curve analysis (Supplemental Figure 1) revealed that underweight and normal patients who had >50 percent increase in delta BMI, had 12.5 (1.69-92) times

higher odds of MetSyn compared to those with a smaller delta BMI (<50); and the odds were 43 (5.8-315) times for those with delta BMI of 108 percent (Table 3).

**Table 3**

Metabolic syndrome by nutritional status at diagnosis and Delta BMI

BMI at Diagnosis	Prevalence of MetSyn		p value	OR (95% CI) of MetSyn when Delta BMI $\geq$ 50
	Delta BMI <50	Delta BMI >50		
Under-weight, Normal (N=428)	7.4% (28/377)	23.5% (12/51)	0.0002	12.5 (1.7-92.2)
Overweight, Obese (N=72)	27% (16/58)	35% (5/14)	0.5	2.0 (0.6-8.1)

BMI, body mass index; OR, odds ratio; CI; confidence interval. Delta BMI is percent change in BMI z-score from diagnosis to evaluation.

## ***Risk Factors for MetSyn and its individual components***

Of the various risk factors studied, multivariable analysis revealed older age at diagnosis (OR 2.78, 1.43-5.4), longer survival duration (OR 2.74, 1.43-5.26), high BMI (obese) at diagnosis (OR 3.2, 1.64-6.2) and high delta BMI (OR 2.26, 1.13-4.55) to be independent predictors of MetSyn (Table 4, supplemental Table 2).

**Table 4**

Univariate and multivariable logistic regression analysis: risk factors for metabolic syndrome

Variable	Univariate			Multivariable		
	OR	95% CI	P	OR	95% CI	P
Gender Female	1					
Gender Male	2.4	1.1-5.4	0.04	1.93	0.83-4.52	0.13
Age at diagnosis <10 years	1.0					
Age at diagnosis 10-18 years	2.9	1.6-5	0.00	2.78	1.43-5.4	0.00
Age at eval <18 years	1.0					
Age at eval ≥18 years	3.7	2.0-14.5	0.82			
Survival time from diagnosis < 10 years	1.0					
Survival time from diagnosis ≥ 10 years	2.2	1.3- 3.8	0.00	2.74	1.43-5.26	0.00
BMI at diagnosis, underweight, normal	1.0					
BMI at diagnosis, Obese, overweight	3.2	1.5-6.9	0.00	3.19	1.64-6.2	0.00
Delta BMI <50	1					
Delta BMI ≥50	3.15	1.7-5.9	0.00	2.26	1.13-4.55	0.02
Primary Diagnosis						
Hematological malignancy	1.0					
Solid tumor & brain	0.7	0.4-1.4	0.32			
Treatment exposure*						
Chemotherapy	1.0					
Steroid	0.9	0.6-1.7	0.90			
Surgery	0.6	0.3-1.2	0.17			
RT	1.7	1-2.9	0.07			
BMT	1.2	0.3-5.5	0.81			
OR, Odds ratio; CI, confidence interval; P, p-value; eval, evaluation; BMI, body mass index; RT, radiotherapy; BMT, bone marrow transplant.* All patients received chemotherapy.						

Results of chemotherapy exposure showed that use of steroids, anthracycline (>120mg/m<sup>2</sup>), alkylators or antimetabolites did not influence the occurrence of MetSyn. Patients receiving RT at various sites (cranial, abdominal or pelvic), had similar prevalence of MetSyn. Childhood cancer survivors with ALL treated with cranial RT (CRT) had a low OR (1.9, 0.85-4.24) for developing MetSyn, except in very young children (≤ 5 years), OR (5.48, 1.5-20), p, 0.01), when compared to those not exposed to CRT of the same age.

On multivariable analysis, adjusted OR revealed that HT (OR 3.9, 1.6-9.6) and obesity (OR 2.1-3.8) were more likely in adult survivors (compared to children); hypertriglyceridemia was more in males than females (OR, 3.8; 1.1-12.6) and IFG was more likely in survivors of solid tumor (OR 3.7, 1.4-9.6). Central obesity (OR 2.4, 1.3-4.7) and low HDL-c (OR 1.7, 1-2.8) were more common in the longer surviving patients (Supplemental Table 2).

## Discussion

The present study demonstrates a high prevalence of MetSyn and its components in long term Asian Indian survivors of various childhood cancers. The prevalence of MetSyn was age dependent (Figure 1), being lower among children and adolescents (6%) and higher among the adult (19%) survivors. The data from published National studies on healthy individuals revealed that the prevalence of MetSyn in children/adolescents (1-3%) and adults of similar age (11-13%) was significantly lower than in the present analysis [25-30]. It is well established that MetSyn increases with increasing age, however the higher prevalence in survivors compared to the healthy population is noteworthy and concerning [29-33].

Furthermore, the prevalence of MetSyn and its components in CCS are known to vary with ethnicity, and duration of follow-up, in addition to age. Compared to published literature from Asia, and Europe (France, Netherlands) the current analysis reveals a higher prevalence of MetSyn and at an earlier age [34, 35]. However, it is lower than that reported from US by the St Jude Lifetime Cohort Study (34%) although they had a much longer follow-up and older age at evaluation [6]. The present study demonstrates a 12.2% prevalence of MetSyn in a cohort of 500 CCS in a tertiary care centre in a LMIC at a median follow-up age of 17 years at evaluation. This is higher than that previously reported from Asia (including India), wherein MetSyn was observed in 1.3-8% of pediatric and 10-12% of adult CCS [36-38]. This may be partly explained due to the fact that these studies had a shorter follow-up and younger age at evaluation. High prevalence of MetSyn at an early age among CCS in our study and its potential adverse implications on health and quality of life reinforces the need for increasing awareness for its early identification. This assumes greater significance as it is often an ignored and underestimated late effect and early institution of preventive strategies and lifestyle modification may significantly delay or reverse the associated long-term morbidities.

## *Components of MetSyn*

Two MetSyn components, low HDL-c (61.8%) and central obesity (33%) were observed in a large number of CCS and were much higher than values reported from HIC [6, 35]. This observation may be explained by ethnic differences in patterns of dyslipidemia and obesity in Asian Indians and also the trend of increasing obesity in LMIC in recent times. Investigators have shown that compared to other ethnic groups, children with ancestral origin in South Asia manifest central adiposity, insulin resistance and metabolic perturbations earlier in life and these derangements are of higher magnitude than white Caucasian children [30]. Both these components are associated with high odds of developing MetSyn

and known to predispose to atherosclerotic heart disease [6, 31, 35]. Therefore, regular assessment of these individual components may aid in early identification of CCS at risk of developing MetSyn. This may also facilitate streamlining ACT activity and allocation of adequate manpower and resources to institute frequent monitoring, and counselling for aggressive risk-reduction strategies.

## ***The risk factors***

### **Delta BMI**

It is well established that obesity is the central factor in the pathogenesis of insulin resistance and MetSyn [35]. However, it is noteworthy that most of our CCS who developed MetSyn were non-obese/overweight at diagnosis and a high delta BMI at follow-up strongly predicted MetSyn (OR 12.5[1.7-92]). Our results indicate that an 'increasing trend in BMI' reported as delta BMI may be of greater value, than a 'spot BMI' to look at risk of obesity and MetSyn [18, 32, 33]. Hence we believe that the trajectory of delta BMI should be monitored during follow-up visits to the ACT clinic and any recent large change in BMI should prompt evaluation for MetSyn. Therefore the observed mean increment in BMI z-score as a risk factor for development of MetSyn in CCS needs to be validated in a larger prospective study. Furthermore, it highlights the fact that monitoring should not be limited to only those who are obese/overweight.

Among the other potential risk factors, our study revealed older age at diagnosis, longer survival and high BMI at diagnosis to be the only independent predictors of MetSyn and similar results have been reported by other investigators [6, 35, 39]. While age at diagnosis and survival duration both reflect ageing and its ineliminable consequences, high BMI (obesity) is a modifiable fore-runner of MetSyn.

Although we observed a higher prevalence of MetSyn and hypertriglyceridemia in males, on univariate analysis, sex was not found to be an independent prognostic factor. While the French L.E.A. study has reported a higher incidence in males [35], the St Jude Life Time Cohort Study found a higher prevalence in females, although statistically non-significant [6]. Another study in Asian Indians by Mohapatra et al has also observed male predominance [36]. Gender bias and preferential male treatment (overprotectiveness and overfeeding) in this part of the world may have been a contributory factor.

We observed the prevalence of MetSyn to be similarly high across the spectrum of various childhood cancers (10-16%), including ALL survivors (12%) (Table 1). Hence, type of primary cancer as also the nature of treatment exposure did not significantly influence risk of MetSyn. Others have reported survivors of sarcomas, germ cell tumors, those treated with abdominal RT and BMT to be at higher risk of MetSyn. Furthermore, published studies have implicated CRT in patients with brain tumor and ALL as risk factors for the development of MetSyn [6, 34, 40-42]. Despite having a large cohort of ALL survivors we were unable to elicit cranial RT as a risk factor. The primary mediator of MetSyn associated with CRT is believed to be growth hormone deficiency leading to obesity and dyslipidemia and has been reported with

RT doses of 18-24 Gy for ALL and  $\geq 25$  Gy for brain tumor. The CRT doses administered to majority of our ALL patients was lower (12.6 Gy) and may explain our observation that, except for exposure to CRT in very young children ( $\leq 5$  years) with ALL, we did not observe it to be a risk factor. Furthermore, our cohort included small numbers of survivors of brain tumor and BMT that precluded meaningful analysis.

The main limitation of our study is that it was a cross-sectional cohort study and lacked serial, annual BMI assessments during follow-up. Furthermore we did not have age- and sex-matched control group for comparison. Nonetheless it has a number of strengths, it is one of the largest studies from a single LMIC centre wherein MetSyn was classified based on IDF criteria. It provides valuable insight into the risk factors of MetSyn in CCS and highlights the novel predictive role of delta BMI in LMIC.

## Conclusion

The present study demonstrates Asian Indian CCS to be at high risk for MetSyn and its components at an early age. Obesity and dyslipidemia were the two major contributing factors for its development and are both modifiable with lifestyle changes. Monitoring delta BMI during follow-up can be a useful tool for early identification of non-obese/overweight CCS, at risk of MetSyn that needs validation in larger longitudinal cohort. Due to the manifold increased risk of morbidity and mortality as a consequence of MetSyn, there is an overwhelming medical and ethical imperative for its early detection and timely intervention. Further research into the genetic landscape of MetSyn may help to better predict risk and individualize cancer treatment thereby leading to lower toxicities in the future.

## Abbreviations

<b>Abbreviation</b>	<b>expanded form</b>
MetSyn	Metabolic syndrome
CCS	Childhood cancer survivors
LMIC	Lower middle-income countries
BMI	Body mass index
WC	Waist circumference
IDF	International Diabetes Federation
TGs	Triglycerides
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
HDL-c	High-density lipoprotein cholesterol
IFG	Impaired fasting glycemia
HT	Hypertension
SD	standard deviation
IQR	Inter quartile range
ANOVA	Analysis of variance
OR	Odds ratio
ROC	Receiver operating characteristic
CI	Confidence interval
ALL	Acute lymphoblastic leukemia
RT	Radiotherapy
CRT	Cranial radiotherapy
BMT	Bone marrow transplant
ACT	After completion of therapy

## Declarations

### • Funding:

Not applicable

- **Conflicts of interest/Competing interests:**

none

- **Ethics approval (include appropriate approvals or waivers):**

The study was approved by the ethical committee of the institute

- **Consent to participate:**

Informed consent was obtained from all individual participants/guardians included in the study.

- **Consent for publication:**

The participant has consented to the submission of the data in the manuscript to the journal.

- **Availability of data and material (data transparency):**

present

- **Code availability (software application or custom code):**

not applicable

- **Disclosure:**

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- **Authors' contributions:**

AA: Data collection, analysis of data, writing the first draft manuscript

GK: Designing and conceptualizing the study, analysis and interpretation of data, drafting the manuscript, proofreading manuscript

SJ: Drafting and proof-reading the manuscript

PM: Drafting and proofreading the manuscript

AS: Data analysis and statistics for the study

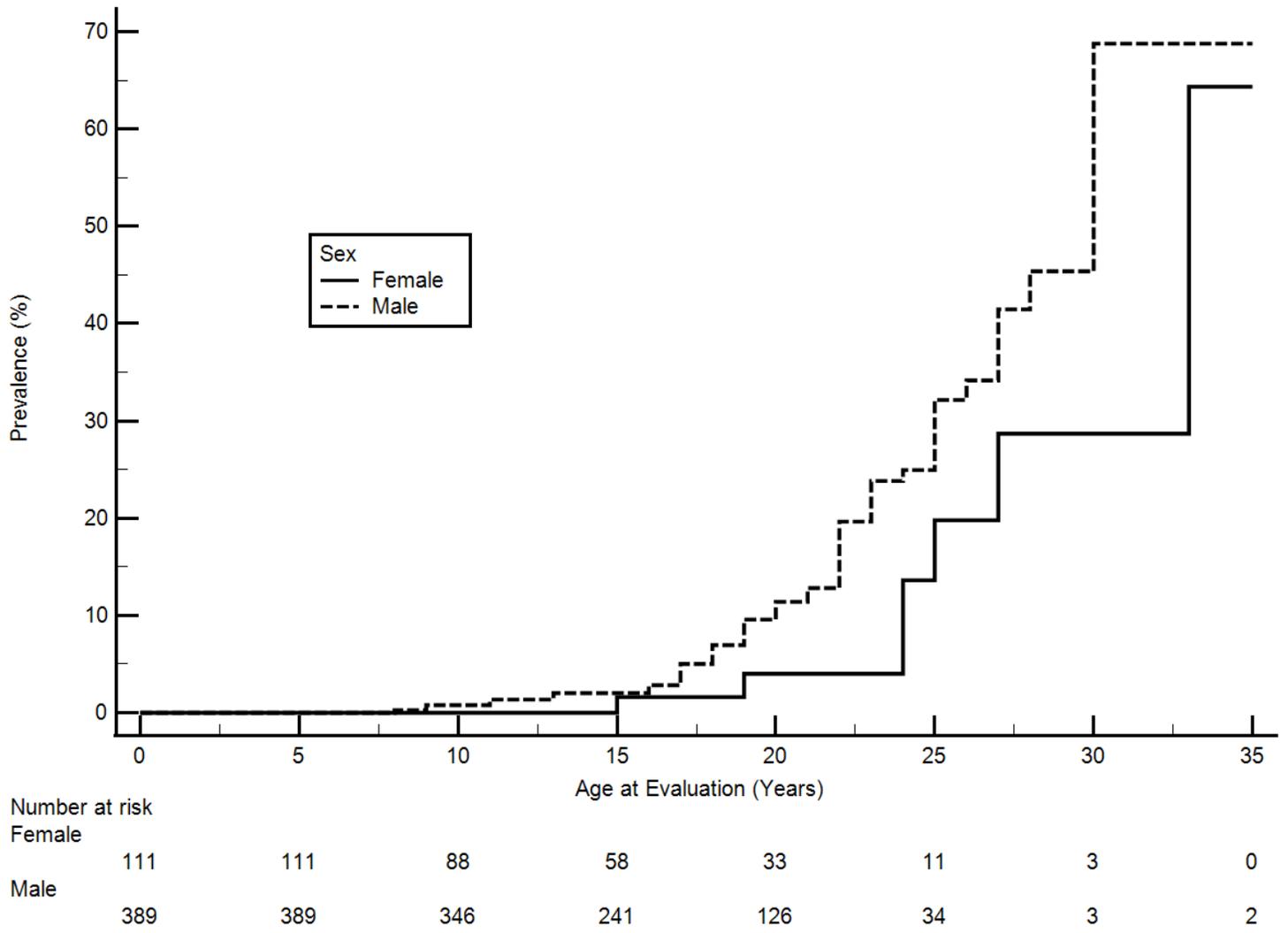
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## Figures



**Figure 1**

Age and sex specific prevalence (%) of metabolic syndrome (MetSyn) as defined by the International Diabetes Federation criteria.

## Supplementary Files

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