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ORIGINAL ARTICLE

# Relapse in children with clinical stage I testicular yolk sac tumors after initial orchiectomy

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## Abstract

**Purpose** To evaluate risk factors of relapse in pediatric patients with clinical stage I (CS1) testicular yolk sac tumors.

**Methods** With retrospective analysis, the medical records of children with pure testicular yolk sac tumors who were referred to Sun Yat-sen University Cancer Center and The First Affiliated Hospital from January 1995 to December 2015 were selected and recorded. Histopathology and staging were retrieved and multivariate analysis was performed with SPSS 20.0 software.

**Results** 90 children with CS1 testicular yolk sac tumors were selected, and 21 of them underwent chemotherapy following initial orchiectomy. The median age of them was 17 months. With a median follow-up of 61 months (range 11–183 months), 84 patients were alive and 3 patients died, whereas the status was unknown in 3 patients. 30 patients experienced relapse within a median time of 4 months, including only 1 patient who underwent primary chemotherapy, and 28 of these patients underwent salvage chemotherapy. According to adjusted analysis, lymphovascular invasion (LVI) ($P<0.001$), necrosis ($P=0.003$) and primary chemotherapy ($P=0.008$) were independent predictors of event-free survival. The 4-year event-free survival of high- and low-risk patients was 46.5% and 85.1%, respectively ($P<0.001$).

**Conclusions** LVI and necrosis were independent risk factors for relapse in pediatric patients with CS1 testicular yolk sac tumors, and primary chemotherapy was effective. Thus, individualized management might be feasible for these patients according to risk classification.

**Keywords** Yolk sac tumor · Testicular cancer · Pediatric · Relapse · Risk factor

## Abbreviations

| | |
|---|---|
| CS1 | Clinical stage I |
| LVI | Lymphovascular invasion |
| RPLND | Retroperitoneal lymph node dissection |
| YST | Yolk sac tumor |
| RIO | Radical inguinal orchiectomy |
| GCT | Germ cell tumor |
| NSGCT | Nonseminomatous germ cell tumor |
| PEB | Cisplatin, etoposide and bleomycin |
| EP | Etoposide and cisplatin |
| PVB | Cisplatin, vinblastine and bleomycin |
| VIP | Etoposide, ifosfamide and cisplatin |
| OS | Overall survival |
| EFS | Event-free survival |

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## Introduction

Yolk sac tumors are the most common type of malignant pediatric testicular tumor, and since 70–80% of patients present with clinical stage I (CS1) disease, patients tend to have positive outcomes [1–6]. Due to its predilection for hematogenous metastasis in children, primary retroperitoneal lymph node dissection (RPLND) is not recommended for CS1 yolk sac tumors (YSTs), but radical inguinal orchiectomy (RIO) has been shown to be effective [1, 6, 7]. In contrast, in some reports, chemotherapy was advocated to prevent recurrence after RIO for early-stage disease, and adjuvant chemotherapy was linked to a reduction in recurrence and an improvement in survival of patients with stage II disease (POG/CCG staging system) [8–12]. For CS1 pediatric testicular germ cell tumors (GCTs), surveillance is recommended, and chemotherapy is performed when progression is detected. In contrast, salvage chemotherapy for children can result in long-term toxicity, including cardiovascular disease, neurotoxicity, ototoxicity, chronic kidney disease, infertility and secondary malignancy [12–14].

In adult CS1 nonseminomatous germ cell tumors (NSGCTs), risk-adapted treatment has traditionally been performed according to the presence of certain risk factors such as vascular invasion, while 1–2 courses of chemotherapy with cisplatin, etoposide and bleomycin (BEP) have been recommended for high-risk patients. As Schlatter reported in one study, nearly 20% (11/63) of boys with CS1 testicular germ cell tumors experienced disease progression, although they were cured with further chemotherapy [1]. Therefore, determining the risks of relapse for CS1 disease has been critical in the stratification of pediatric testicular cancer. The investigation of risk factors in adults with CS1 NSGCTs demonstrated that lymphovascular invasion (LVI) and a high percentage of embryonal carcinoma as a tumor component were high-risk features for relapse; these features were also useful in risk stratification of their pediatric and adolescent counterparts [15–17]. However, the risks of relapse in children with CS1 testicular YSTs, which are the most common malignant GCTs in children, were not analyzed independently. Based on the risk factors, the high-risk group of patients could receive a lower dose of primary chemotherapy with a lower toxicity, although the long event-free survival rates that have been observed after salvage chemotherapy are encouraging.

The aim of this study is to investigate pediatric testicular YSTs in two high-volume medical centers in South China, Sun Yat-sen University Cancer Center and The First Affiliated Hospital and to evaluate the risks of tumor relapse in patients with CS1 disease. This investigation may help boys with CS1 yolk sac tumors receive treatment according to risk stratification.

## Methods

This retrospective study was approved by the Sun Yat-sen University Cancer Center Ethics Committee (No. 2016-FXY-081). Between January 1995 and December 2015, 182 children (≤ 12 years of age) were referred to these two centers for testicular tumors. Clinical data, including age, presentation, serum markers (AFP, β-HCG and LDH), images (CT or MRI scan), treatment and follow-up were recorded and retrospectively analyzed. Pathological results, especially regarding lymphovascular invasion and necrosis, were retrieved. Clinical staging was confirmed according to the POG/CCG system, and tumor necrosis was defined as microscopic coagulative necrosis that could be recognized by pathologists regardless of the size or number of necrotic lesions. Moreover, patients whose AFP level did not return to normal or who were diagnosed with tumors other than pure yolk sac tumors were excluded.

All patients underwent RIO. Primary RPLND was performed in two patients during an earlier study period, but this has been rare in the last 10 years. Primary chemotherapy was performed in patients with progression potential including a tumor size > 3.0 cm, LVI and a serum AFP level > 10 000 ng/mL. Chemotherapy regimens included PEB (cisplatin-DDP, 20 mg/m$^2$, d1–5; etoposide, 100 mg/m$^2$, d1–5; bleomycin, 10–15 mg/m$^2$, d1; administered at 3-week intervals), EP (etoposide, 100 mg/m$^2$, d1–5; cisplatin, 20 mg/m$^2$, d1–5; administered at 3-week intervals), and PVB (cisplatin, 20 mg/m$^2$, d1–5; vinblastine, 20 mg/m$^2$, d1, d5; Bleomycin, 10–15 mg/m$^2$, d1; administered at 3-week intervals). During the study years, the cycles and regimens were not consistent all the time. Salvage chemotherapy was recommended when relapse was detected. PEB, PVB and VIP (etoposide, 75 mg/m$^2$, d1–5; ifosfamide, 1.2 g/m$^2$, d1–5; cisplatin, 20 mg/m$^2$, d1–5; administered at 3-week intervals) were administered for 3–6 cycles.

Close follow-up including physical examination, assessment of serum markers and imaging including chest X-ray, abdominal CT or ultrasound was required for all patients. Such follow-up was performed every 3–4 months during the first 2 years, then annually. When relapse was suspected, serum AFP was evaluated first.

Remote interviews were performed by telephone and included information on the children's overall status, development, and treatment after discharge. Using SPSS 20.0 statistical software (SPSS, Inc., Chicago, IL, USA), potential risk factors were evaluated by the Cox-regression method. Correlations between clinical-pathological features, including serum AFP, Ki67, lymphovascular invasion, necrosis, size, age, relapse status and different treatments were analyzed using the Chi-square test. Subsequently, patients were divided into two groups: high risk (with one or more risk

factors) and low risk (without any risk factor). The survival rates were calculated according to the Kaplan–Meier method and were compared using the log-rank test. $P < 0.05$ was considered statistically significant.

## Results

Over a period of 21 years, 92 pediatric patients with CS1 testicular yolk sac tumors were treated at the Cancer Center and The First Affiliated Hospital of Sun Yat-sen University. Two of them treated with primary RPLND were excluded. This study included 69 patients who underwent active surveillance and 21 who underwent primary chemotherapy. The patients ranged in age from 4 to 58 months and had a median age of 17 months. The median AFP level at presentation was 5346 ng/mL (range from 252 to > 121,000 ng/mL). The clinical characteristics of the patients are shown in Table 1.

In all, 69 patients returned regularly to these two hospitals for follow-up. Remote interviews by telephone were accomplished with 87 patients by October 2016; the other 3 patients did not complete follow-up. The median follow-up time was 61 months (range 11–183 months). During follow-up, 30 patients experienced relapse within a median time of 4 months (range 1–27 months), including 1 patient who underwent chemotherapy and 29 who underwent RIO alone.

**Table 1** Clinical characteristics of all patients

| Characteristics | Number (relapse) | | *P* value |
|---|---|---|---|
| | Surveillance | Chemotherapy | |
| Serum AFP level (252- > 121000) | | | |
| ≤ 10,000 ng/ml | 53 (23) | 18 (1) | 0.381 |
| > 10,000 ng/ml | 16 (6) | 3 (0) | |
| Ki67 | | | |
| ≤ 60% | 57 (25) | 21 (1) | 0.061 |
| > 60% | 12 (4) | 0 (0) | |
| Lymphovascular invasion | | | |
| Absent | 55 (17) | 14 (0) | 0.216 |
| Present | 14 (12) | 7 (1) | |
| Necrosis | | | |
| Absent | 51 (18) | 14 (0) | 0.516 |
| Present | 18 (11) | 7 (1) | |
| Size (1.0–7.0 cm) | | | |
| ≤ 3 cm | 36 (16) | 8 (0) | 0.258 |
| > 3 cm | 33 (13) | 13 (1) | |
| Age (0.3–5.0 years) | | | |
| ≤ 2 years | 52 (16) | 18 (0) | 0.318 |
| > 2 years | 17 (13) | 3 (1) | |
| Relapse | | | |
| Absent | 40 | 20 | 0.002 |
| Present | 29 | 1 | |

Of the 30 patients with relapse, 28 of them followed up with salvage chemotherapy.

The other 2 patients who refused chemotherapy died 9 and 12 months after relapse, respectively. One patient who did not receive primary chemotherapy progressed after salvage chemotherapy and died 21 months after relapse, even though second-line chemotherapy using a VIP regimen was given. In all, 84 patients survived, 3 patients died, and the status of 3 patients was unknown. For the patients with relapse, 12 had disease that was confined to the retroperitoneal lymph nodes, 6 had distant metastases, 8 showed involvement of the retroperitoneal lymph nodes and distant organs, and the other 4 demonstrated elevated AFP levels but did not have apparent metastatic lesions.

Event-free survival (EFS) at 4 years was 66.7%, and overall survival (OS) was 97.8% (Fig. 1). 4-year EFS for patients who underwent chemotherapy and for those who underwent surveillance was 95.2% and 58.0%, respectively (Fig. 2, $P < 0.001$). According to the unadjusted analysis, LVI and necrosis were associated with poor EFS, whereas primary chemotherapy and age (≤ 2 years of age) were correlated with better EFS. Additionally, LVI ($P < 0.001$), necrosis ($P = 0.003$) and primary chemotherapy ($P = 0.008$) were independent predictors of EFS (as shown in Table 2). The patients were then divided into the following two groups: the high-risk group, which presented with LVI and/or necrosis, and the low-risk group,

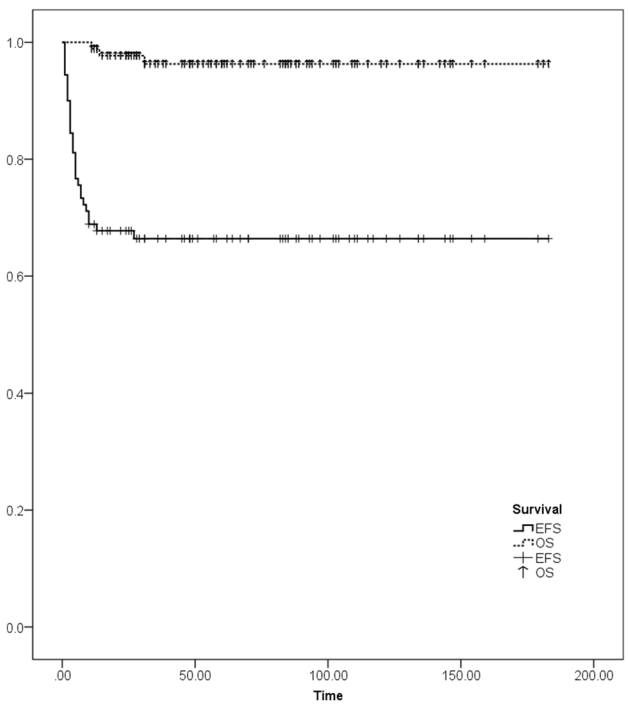


**Fig. 1** Event-free survival and overall survival of CS1 pediatric testicular yolk sac tumor. *EFS* event-free survival, *OS* overall survival

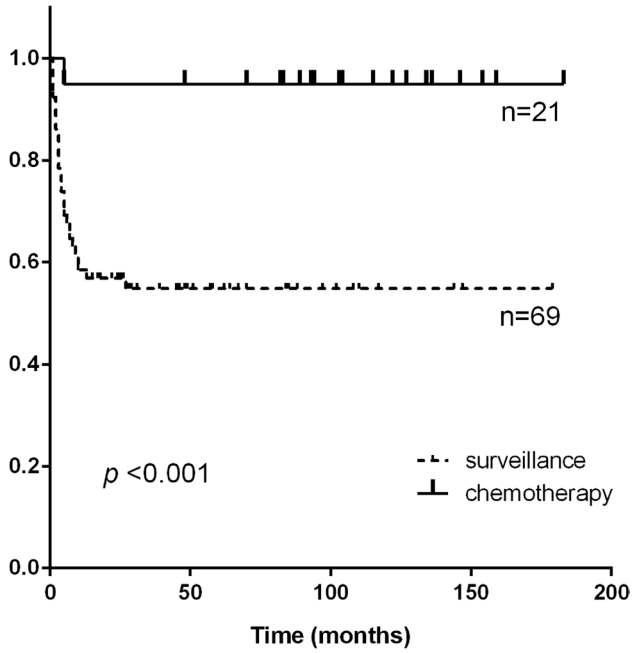


**Fig. 2** Event-free survival of patients who underwent primary chemotherapy and surveillance

which did not present with LVI or necrosis. The 4-year EFS in the high-risk and low-risk groups was 46.5% and 85.1%, respectively ($P < 0.001$) (Fig. 3). In the high risk group, chemotherapy improved the EFS significantly, while in the low risk group, the effectiveness was limited (Fig. 4, $P = 0.0002$ and 0.2144, respectively).

In patients who underwent active surveillance, the 4-year EFS and the OS were 58.0% and 95.7%, respectively. The 4-year EFS in the high-risk and low-risk groups, was 26.7% and 82.1%, respectively ($P < 0.001$).

## Discussion

Despite the low incidence of pediatric testicular tumors, YSTs, which are the most common malignant type of testicular tumor in children, are different from their counterpart in adults [18, 19]. Nearly all malignant testicular tumors in prepubertal children are pure yolk sac tumors, and hematogenous metastasis is as common as retroperitoneal metastasis in cases of advanced disease [7, 17]. In the most recent report of CS1 malignant testicular GCTs in boys age > 10 years, mixed histology and the presence of LVI were found to be associated with relapse after orchiectomy [17]. Although the overall survival of these patients was 100%, the 4-year EFS for patients with pure YSTs was 81%. Chemotherapy, including 3 cycles of compressed PEB, was given to boys with relapse. In a model of prognostic factors for pediatric extracranial GCTs, tumor site, stage and age were predictors of overall outcome, but the serum AFP level and YST histology were not significant factors [20].

In this study, 30 patients experienced relapse during surveillance, and regional metastasis was observed in approximately 40%, which was similar to what was found in prior studies; this also implied that half of those who experienced relapse had stage IV disease [7, 17]. LVI, necrosis and primary chemotherapy were considered independent predictors of relapse. This study confirmed that LVI was an indicator of a poor prognosis in patients with CS1 testicular cancer and that primary chemotherapy could significantly improve event-free survival. In addition, this study demonstrated that necrosis was an important predictor of relapse, which might be useful for risk-adapted management. In cancer of the renal pelvis, necrosis is an independent predictor of clinical outcome and is associated with pathological features, although controversial results have been presented [21, 22]. A recent study showed that rete testis and/or epididymis invasion and necrosis might be associated with a poor outcome, but statistical analysis was unavailable in that report, which included a small patient population [5]. To our knowledge, this study

**Table 2** Unadjusted and adjusted analysis of EFS

| Characteristics | Unadjusted analysis *P* value | Adjusted analysis | | |
|---|---|---|---|---|
| | | *P* value | Hazard ratio | 95% CI |
| Serum AFP level | 0.851 | | | |
| Ki67 | 0.930 | | | |
| Size | 0.668 | | | |
| Lymphovascular invasion | *0.002* | *< 0.001* | 0.218 | 0.103–0.462 |
| Necrosis | *0.039* | *0.003* | 0.322 | 0.152–0.685 |
| Age | *0.037* | 0.258 | | |
| Primary chemotherapy | *0.002* | *0.008* | 15.203 | 2.049–112.792 |

Statistically significant *P* values are in italics

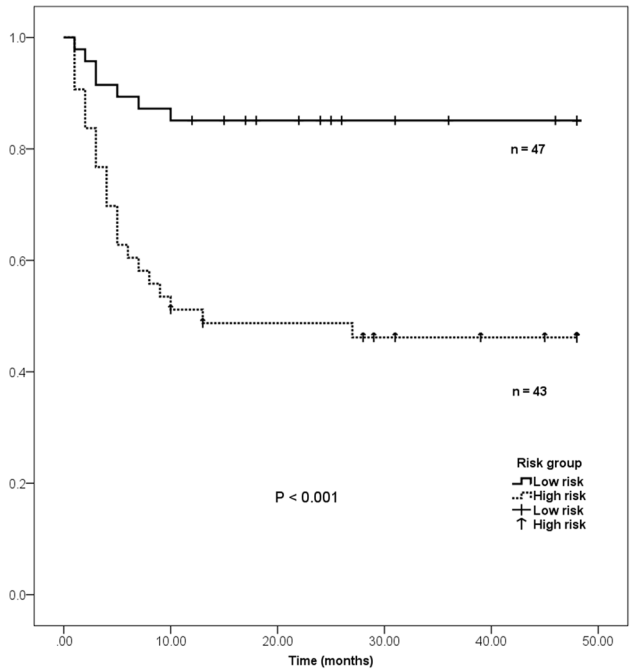


**Fig. 3** Comparison of 4-year event-free survival of groups with low and high risk for CS1 pediatric testicular yolk sac tumor. High risk—LVI and/or necrosis, low risk—no LVI or necrosis

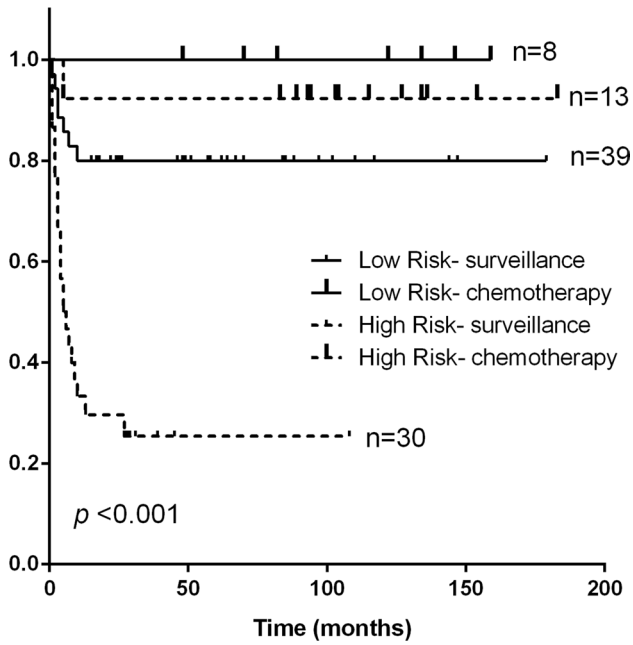


**Fig. 4** Event-free survival of patients who underwent primary chemotherapy and surveillance stratified by risk groups. Low risk—chemotherapy, $n=8$; high risk—chemotherapy, $n=13$; low risk—surveillance, $n=39$; high risk—surveillance, $n=30$

is the first report that has confirmed the prognostic value of necrosis in pediatric testicular cancer.

Although all patients were younger than 5 years of age, we divided them into two groups with 2 years of age as a cut-off according to an incidence curve. Patients ≤ 2 years of age were less likely to experience relapse than those > 2 years of age. However, age was not an independent risk factor for EFS according to the multivariate analysis. In recent studies, the number of patients with testicular YSTs ranged from 22 to 90 cases, and the prognostic factors for CS1 disease were not analyzed separately [5, 9, 17]. Therefore, the characteristics of YSTs might be included when this tumor type is mixed with other types of GCTs. Without disturbances due to age (> 11 years of age), tumor site, stage and histology in prior studies, the statistical results might be more reliable in this study. The serum AFP level, tumor size and Ki67 expression were not associated with tumor relapse, which is consistent with the results of other studies.

For patients who underwent active surveillance, the EFS was significantly lower than for those who underwent primary chemotherapy. The high risk subgroup had a much worse EFS than that of all other patients. For all high risk patients, chemotherapy was also associated with better EFS, similar to the results for the cohort as a whole. In contrast, for the low risk group, the role of chemotherapy was not statistically significant, though chemotherapy was associated with better survival. This finding implied that LVI and necrosis were useful predictors of EFS and that primary chemotherapy was effective.

For pediatric CS1 testicular cancer, the POG/CCG system has suggested surveillance in recent years [17]. However, nearly 90% of malignant testicular tumors in children are yolk sac tumors, and the identification of patients at risk for relapse is critical to the management of CS1 testicular cancer. Considering the nearly 50% relapse rate in high-risk patients, 1–2 cycles of primary chemotherapy may be beneficial, as opposed to a full dose of salvage chemotherapy [23, 24]. Although no research has yet determined whether primary chemotherapy, as opposed to salvage chemotherapy, is linked to lower toxicity or whether these two treatment modalities lead to comparable oncological outcomes, risk-adapted therapy in adults has been shown to produce favorable effects [25, 26]. In one study with a median follow-up of 8.1 years, one course of adjuvant BEP led to a relapse rate of 2.3% for adult CS1 testicular NSGCTs [25]. In a recent report of pediatric GCTs, it was shown that a regimen of low-dose DDP and no Bleomycin resulted in favorable outcomes and that EP was also effective for pediatric testicular GCTs [27]. Additionally, compressed BEP chemotherapy for relapse of testicular GCT has been reported to be effective, as the 4-year overall survival rate was 100% [10, 17]. For pediatric patients, who are expected to have long lives, extreme long-term toxicity and effects, including renal and

gonadal function, infertility and the potential for secondary malignancies, should be taken into consideration [12, 28]. It is possible that risk-adapted primary chemotherapy could further reduce the toxicity in pediatric patients with CS1 testicular YSTs without compromising the oncological outcome. However, most of the high-risk patients would experience relapse and would benefit from primary chemotherapy; the others would be overtreated. Therefore, it is critical to differentiate high risk patients from low risk patients as accurately as possible, according to prognostic predictors.

In this study, the 4-year OS and EFS rates were 97.8% and 66.7%, respectively, which were slightly lower than what was reported in other recent studies. The refusal of salvage chemotherapy by two patients whose parents declined chemotherapy for their children resulted in their death due to tumor progression. In addition, in the current study, the proportion of relapse was higher than in prior reports, which might be due to the bias of tiered medical services. This bias may have resulted in the treatment of several early-stage patients at primary hospitals; they were then referred to these two centers when recurrent and progressive disease was detected.

For studies of minor populations, those that include patients with limited follow-up and those of a retrospective nature, limitations are inevitable. Determining whether risk-adapted treatment leads to less toxicity and comparable oncological outcome requires prospective clinical research. The treatment protocol, which included indications for primary chemotherapy, was also not consistent during this long-term study.

## Conclusions

This study determined that LVI, necrosis and absence of primary chemotherapy were independent risk factors for relapse in pediatric patients with CS1 testicular YSTs. Individualized management according to predictors might demonstrate a favorable balance between oncological outcome and toxicity.

**Data Availability** The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (http://www.researchdata.org.cn), with the approval RDD number as RDDA2017000163.

### Compliance with ethical standards

**Conflict of interest** No conflict of interest was declared.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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