Original Article

Analysis of *RAS* gene mutations in adverse events during first induction chemotherapy in childhood acute lymphoblastic leukemia

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Background: The rat sarcoma virus (*RAS*) pathway controls cell proliferation, differentiation, and apoptosis, which have been implicated in the pathogenesis of various hematological malignancies. Prognostic importance of *RAS* gene mutation, relatively frequently in childhood acute lymphoblastic leukemia (ALL), has been debated. We aimed to study *RAS* gene mutation profile and prognosis in 93 children with newly diagnosed ALL.

Methods: We retrospectively analyzed clinical characteristics, treatment, and outcomes of 93 ALL children during first induction chemotherapy in Anhui Provincial Children's Hospital under the Chinese Children's Leukemia Group-acute lymphoblastic leukemia 2018 (CCLG-ALL-2018). All genomic DNA samples were obtained from bone marrow mononuclear cells upon new diagnosis. *RAS* gene mutation was performed by polymerase chain reaction (PCR). All children were stratified into standard-, medium-, and high-risk groups, and then treated with risk-based regimens according to CCLG-ALL-2018 protocol.

Results: Of 93 ALL children, 26 (27.9%) were positive for *RAS* mutation, among whom 19 had N-*RAS* mutation, 8 had K-*RAS* mutation, and 1 had a double mutation. The *ETV6/RUNX1* fusion gene was the most common genetic alteration (n=16, 17.2%). The most common adverse events during first induction chemotherapy were coagulation abnormalities (n=76, 81.7%), followed by fever (n=71, 76.3%) and alanine transaminase (ALT) elevation (n=34, 36.6%). Compared with negative *RAS* mutation group, the risk of hyperbilirubinemia was significantly reduced in *RAS* mutation group (P=0.018), and there was no significant difference in any other adverse events. The average duration of agranulocytosis during first induction chemotherapy was 6 days, and the average duration of agranulocytosis in *RAS* mutation group and *RAS* negative group was 6 and 5 days, with no significant difference. Multivariate linear regression analysis showed that in *RAS* mutation group, when body mass index (BMI) exceeded the median value of this ALL population (BMI >15.38), the risk of agranulocytosis was significantly increased (P=0.003).

Conclusions: Newly diagnosed ALL in children with *RAS* mutation is less likely to be associated with fusion gene expression. *RAS* mutation increases the risk of agranulocytosis duration during first induction chemotherapy, lowers BMI and reduces the risk of hyperbilirubinemia in ALL children.

Keywords: *RAS* gene mutations; adverse events; first induction chemotherapy; acute lymphoblastic leukemia (ALL)

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy originating from lymphoid precursors (1). If the infiltration of leukemic cells in the central nervous system and subsequent formation of brain tumors occur, the overall survival is still exceptionally low. The CNS involvement is more common in ALL than in adult acute myeloid leukemia (2). Long-term outcomes in childhood ALL have improved over the past half century, largely due to the greater precision in the risk stratification of patients based on the initial diagnostic risk factors and the early treatment response as assessed by minimal residual disease (MRD) (3-5). In addition, the identification of genetic abnormalities associated with prognosis and treatment, along with effective targeted therapies, also plays an important role (6). With the development of gene chip technology and next-generation gene sequencing, an increasing number of genes closely associated with the occurrence and development of childhood ALL are being identified (7).

Rat sarcoma virus (*RAS*) genes are important proto-oncogenes in cells and consist of 3 independent genes: N-*RAS*, K-*RAS*, and H-*RAS*. The *RAS* gene encodes *RAS* proteins, which belong to the small G protein family, regulate signal transduction by binding to a variety of cell membrane receptors, and play an important role in physiological processes such as cell proliferation, differentiation, and apoptosis (8). In many adult tumors, such as colon cancer, lung cancer, and melanoma, *RAS* gene activating mutations are considered to be important oncogenic events in tumor formation (9-11). However, the relationship between RAS and chemotherapy remains elusive. Jerchel *et al.* found RAS-related mutations (*N-RAS*, *K-RAS*, *FLT3* and *PTPN11*) in 44.2% of 461 samples obtained from children with ALL at the time of initial diagnosis (12). The prognostic relationship between *RAS* genes and hematologic tumor diseases in children has recently attracted attention. In this study, we retrospectively analyzed the relationship between *RAS* gene mutations and the incidence of various adverse events during first induction chemotherapy in 93 children with newly diagnosed ALL and investigated the impact of *RAS* gene mutations on leukemia treatment and prognosis. We present the following article in accordance with the REMARK reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-683/rc).

Highlight box

Key findings

- Compared with negative *RAS* mutation group, the risk of hyperbilirubinemia was significantly reduced in *RAS* mutation group (P=0.018), while the risk of agranulocytosis was significantly increased (P=0.003) in *RAS* mutation group when the BMI exceeded the median value (BMI >15.38).

What is known and what is new?

- The mechanisms of *RAS* pathway in hematologic malignancies have been extensively studied. However, prognostic significance of *RAS* mutation is controversial in pediatric acute lymphoblastic leukemia (ALL).
- To investigate potential correlation between *RAS* mutations and adverse events during first induction chemotherapy in pediatric ALL, clinical characteristics, treatment, and outcomes of 93 newly diagnosed ALL children during first induction chemotherapy were reviewed. Of them, 26 (27.9%) were positive for *RAS* mutation.

What is the implication, and what should change now?

- *RAS* mutation may increase the risk of agranulocytosis duration during first induction chemotherapy in ALL children with lower BMI.

Methods

Patient cohorts

A retrospective cohort analysis was conducted on 93 records of children who were diagnosed with ALL from January 2020 to July 2021 in the Department of Hematology and Oncology in Anhui Provincial Children's and who met the following inclusion criteria: (I) age ≤14 years; (II) meeting the diagnostic criteria set by the recommendations on the Suggestion of diagnosis and treatment of acute lymphoblastic leukemia in childhood (the 4th revised version, Revised by Hematology Group, Pediatrics Branch of Chinese Medical Association) (11); and (III) diagnosed with ALL for the first time (did not receive any drug chemotherapy, including glucocorticoids, before the first induction chemotherapy). The exclusion criteria were the following: (I) children with unclear diagnosis; (II) children not diagnosed with ALL for the first time; (III) children who had received induction chemotherapy or nonstandard treatment in other hospitals; (IV) children who were transferred to the hospital during the first induction chemotherapy but did not complete the induction treatment; and (V) children who voluntarily abandoned treatment for non-disease-related reasons. Informed consent was obtained from patient's parents. The study was conducted in accordance with the Declaration of Helsinki (as

Table 1 First induction chemotherapy regimen

Drug	LR	IR and HR
Pred	60 mg/m^2/d, d1–28	60 mg/(m^2·d), d1 25% of total dose, d2 50% of total dose, d3 75% of total dose, d4 100% of total dose, d1–7
VCR	1.5 mg/m^2, once a week, 4 times in total	1.5 mg/m^2, once a week, 4 times in total
DNR	30 mg/m^2, once a week, 2 times in total	30 mg/m^2, once a week, 4 times in total
L-ASP	2,500 U/m^2, d9, d23	2,500 U/m^2, d9, d23

Pred, prednisone; VCR, vincristine; DNR, daunorubicin; L-ASP, L-asparaginase; LR, low risk; IR, intermediate risk; HR, high risk.

revised in 2013). The study protocols were approved by the Ethics Committee of Anhui Provincial Children's Hospital (No. CR20221210).

Mutation analysis of RAS gene alterations

All genomic DNA (gDNA) samples were obtained from bone marrow mononuclear cells at the time of new diagnosis. Polymerase chain reaction (PCR) primers were used to amplify the target genome, which was enriched and sequenced on a NextSeq550 sequencer (Illumina NovaSeq6000, USA). The original data were analyzed and annotated with gene variation information through the optimized biomarker analysis process, and the pathogenic gene mutation sites were finally screened. This test covered point mutations in exonic regions and nearby intronic regions within ±10 bp as well as insertional and deletional mutations within 10 bp of common causative genes in ALL.

Classifications and treatments

All the enrolled participants with ALL were diagnosed according to the diagnostic criteria formulated by the recommendations on the Suggestion of diagnosis and treatment of acute lymphoblastic leukemia in childhood (the 4th revised version, Revised by Hematology Group, Pediatrics Branch of Chinese Medical Association) (13). The risk group assignment was based on age, white blood cell (WBC) count, immune typing, cytogenetic characteristics at diagnosis, and early treatment response and MRD level. All patients were then stratified into the standard risk group, medium risk group, and high-risk group.

The Chinese Children's Leukemia Group-acute lymphoblastic leukemia 2018 (CCLG-ALL-2018) protocol was published in 2018 and is recommended as a clinical guideline for the treatment of pediatric ALL in China. The treatment regimen contains 5 phases, including induction, early reinforcement, consolidation, delayed reinforcement, and maintenance treatments.

All children were treated with risk-based regimens according to the CCLG-ALL-2018 protocol. The main drugs of the first induction chemotherapy regimen included prednisone, vincristine (VCR), daunorubicin (DNR), and L-asparaginase (L-ASP). The specific regimen is illustrated in *Table 1*.

Adverse events

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, all children were classified and evaluated for adverse events during the first induction chemotherapy. The most common adverse events include fever, infection, sepsis, hypotension, hypertension, hypoxia, acute respiratory distress syndrome (ARDS), pancreatitis, hepatotoxicity [elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], hyperbilirubinemia, hyponatremia, and intestinal obstruction and constipation.

Statistical analysis

The software OriginPro 2021 (OriginLab Corporation, Northampton, MA, USA) was used to draw the heatmap of mutant genes. The χ^2 test was used to compare the rates, and the *t* test was used to compare the continuous variables with normal distribution. The Mann-Whitney test was used for continuous variables that did not follow normal distribution, and the χ^2 test was used for categorical variables. Univariate analysis variables with $P<0.1$ were substituted into a binary logistic regression model for multivariate analysis. The competitive risk model R 4.0.3 software (The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. Kaplan-Meier survival analysis, a Cox regression model, and multiple linear regression were used

to explore the relationship between the *RAS* gene mutation and the risk and duration of some adverse events. Univariate analysis variables with P<0.1 were substituted into the Cox regression model for multivariate analysis. P<0.05 was considered statistically significant.

Results

Clinical characteristics and outcomes

A total of 93 children with ALL were enrolled in this study, including 51 males and 42 females. All enrolled patients accepted vincristine + daunorubicin + L asparaginase + prednisone (VDLP) chemotherapy as the first induction chemotherapy. The mean age at consultation was 5.2±3.2 years. There were 11 cases (11.8%) of standard risk children, 62 cases (66.7%) of medium-risk children, and 15 cases (16.1%) of high-risk children. The patients with who turned MRD-negative on the 15th day during the first induction chemotherapy accounted for 37.6% of patients, while patients who turned MRD-negative on the 33rd day accounted for 78.5%. The bone marrow cytological CR rate on the 33rd day was 100%. Other general clinical data are shown in *Table 2*.

Furthermore, 88 patients (94.6%) with ALL completed induction chemotherapy, and other 5 died during induction. One patient died of acute cerebral hemorrhage. One patient died of ARDS due to repeated hypoxemia during chemotherapy. The remaining 3 cases died of septic shock, including 1 case of multidrug-resistant bacteria infection.

RAS mutations in children with ALL

Regarding gene mutations, 32 cases (34.4%) were gene mutation–positive, and 38 cases (40.9%) had bone marrow chromosome abnormalities at initial diagnosis. The most frequent type of fusion gene (n=16, 17.2%) was *ETV6/RUNX1*. The most common genetic alteration (n=26, 27.9%) was the *RAS* gene mutation, including 19 cases of N-*RAS* mutation, 8 cases of K-*RAS* mutation, and 1 case of double mutation, followed by the NOCTH1 gene mutation (n=8, 8.6%). NOTCH1 mutations were detected in 7 cases with Precursor T cell acute lymphoblastic leukemia (T-ALL) and only in 1 case with Precursor B cell acute lymphoblastic leukemia (B-ALL). The distribution of the remaining mutations is shown in the mutant gene heat map (*Figure 1*). It is worth noting that *RAS*-positive samples showed a lower detection rate of fusion genes than did the *RAS*-negative group (P=0.002; *Table 1*).

Statistics of various adverse events in first induction chemotherapy

The occurrence of 23 types of adverse events, including fever, infection, granulopenia, liver function impairment, and intensive care unit (ICU) admission during the first induction chemotherapy of children with ALL was counted in this study. The results showed that the most common adverse events during the first induction of ALL were coagulation dysfunction (n=76, 81.7%), fever (n=71, 81.7%), and elevated ALT (n=34, 36.6%). The risk of hyperbilirubinemia was significantly reduced in the *RAS*-positive group compared with the *RAS*- negative group (P=0.018), and there was no significant difference in the other types of adverse events (*Table 3*).

The median time of emergence of agranulocytosis was 7.57 days during the first induction chemotherapy. The *RAS* mutation-positive subgroup developed neutropenia earlier than *RAS* mutation-negative mutation subgroup (6.38 *vs.* 8.03 days), but there was no significant difference between the two groups (P=0.38). On other hand, as shown in *Table 3*, the duration of agranulocytosis in the *RAS* mutation-positive subgroup was shorter than that in the *RAS* mutation-negative subgroup (18 *vs.* 24 days); similarly, there was no significant difference between the two groups (P=0.14).

On the 33rd day of VDLP induction chemotherapy, routine blood examination revealed that all patients with ALL developed severe agranulocytosis (*Figures 2,3*). The Cox proportional hazards model and multiple linear regression analysis showed that in the *RAS* mutation-negative group, the risk of prolonged agranulocytosis was significantly increased when BMI exceeded the median value of the study population (BMI >15.38; P=0.003; *Figures 4,5*).

Discussion

The *RAS* gene contains 3 different mutant subtypes, which are mainly found in eukaryotes (8,14). N-RAS is located on chromosome 1 (1p22-p32), while H-*RAS* and K-*RAS* are located on chromosome 11 (11p15.1-p15.3) and chromosome 12 (12P1.1), respectively (15). Different subtypes of *RAS* genes are expressed differently in tumors (16). According to the Cancer Somatic Mutation Catalog database, K-*RAS* is the most common mutant subtype in all cancers. The main *RAS* genes of common mutations are located on codon 12,

Table 2 Patients characteristics at diagnosis

Characteristic	All (N=93)	*RAS* positive (n=26)	*RAS* negative (n=67)	P value
Age (years)	5.2±3.2	4.8±3.1	5.3±3.35	0.515
BMI (kg/m^2)	16.30±4.02	15.4±155.2	16.6±4.61	0.333
Blood routine				
WBC (×10^9/L)	66.55±134.97	85.89±22.74	59.05±126.75	0.404
Hb (g/L)	74.30±24.48	74.28±52.18	74.34±25.29	0.901
PLT (×10^9/L)	70.15±65.82	60.65±1.54	73.84±70.43	0.722
Sex				1.000
Male	51 (54.8%)	14 (53.8%)	37 (55.2%)	
Female	42 (45.2%)	12 (46.2%)	30 (44.8%)	
Risk group				0.929
LR	11 (11.8%)	3 (11.5%)	8 (11.9%)	
IR	62 (66.7%)	18 (69.2%)	44 (65.7%)	
HR	15 (16.1%)	3 (11.5%)	12 (17.9%)	
Immunophenotype				0.281
B-ALL	82 (88.2%)	21 (80.8%)	61 (91.0%)	
T-ALL	11 (11.8%)	5 (19.2%)	6 (9.0%)	
MRD status				
D15 MRD <10^{-4}	35 (37.6%)	11 (42.3%)	24 (35.8%)	0.604
D33 MRD <10^{-4}	73 (78.5%)	13 (50%)	54 (80.6%)	0.502
CNS status				0.067
CNSL1	82 (88.2%)	20 (76.9%)	62 (92.5%)	
CNSL2	11 (11.8%)	6 (23.1%)	5 (7.5%)	
CNSL3	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Tumor lysis	4 (4.3%)	1 (3.8%)	3 (4.5%)	1.000
Fusion gene abnormality	32 (34.4%)	2 (7.7%)	30 (44.8%)	0.002*
Chromosome abnormality	38 (40.9%)	15 (57.7%)	23 (34.3%)	0.059
Induction failure death	5 (5.4%)	2 (7.7%)	3 (4.5%)	0.616

The data are shown as n (%) or mean ± standard deviation. *, compared with the *RAS*-negative group, P<0.05. *RAS*, rat sarcoma virus; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; PLT, platelets; LR, low risk; IR, intermediate risk; HR, high risk; B-ALL, Precursor B cell acute lymphoblastic leukemia; T-ALL, Precursor T cell acute lymphoblastic leukemia; MRD, minimal residual disease; CNSL, central nervous system leukemia.

13 and 61, and are somatic mutations (17,18).

As an important signal switch, *RAS* protein molecules participate in the binding and dissociation of guanosine triphosphate/diphosphate (GTP/GDP), which in turn activate downstream of the original activated protein kinase and phosphatidyl inositol-3-kinase/protein kinase β signaling pathway (19,20). This affects cell growth and other life processes, including proliferation, differentiation, and apoptosis, and promotes the occurrence and development of tumors. *RAS* is the most common mutated oncogene in human tumors, and is widely present in hematological tumors, colon cancer, thyroid cancer, gastric

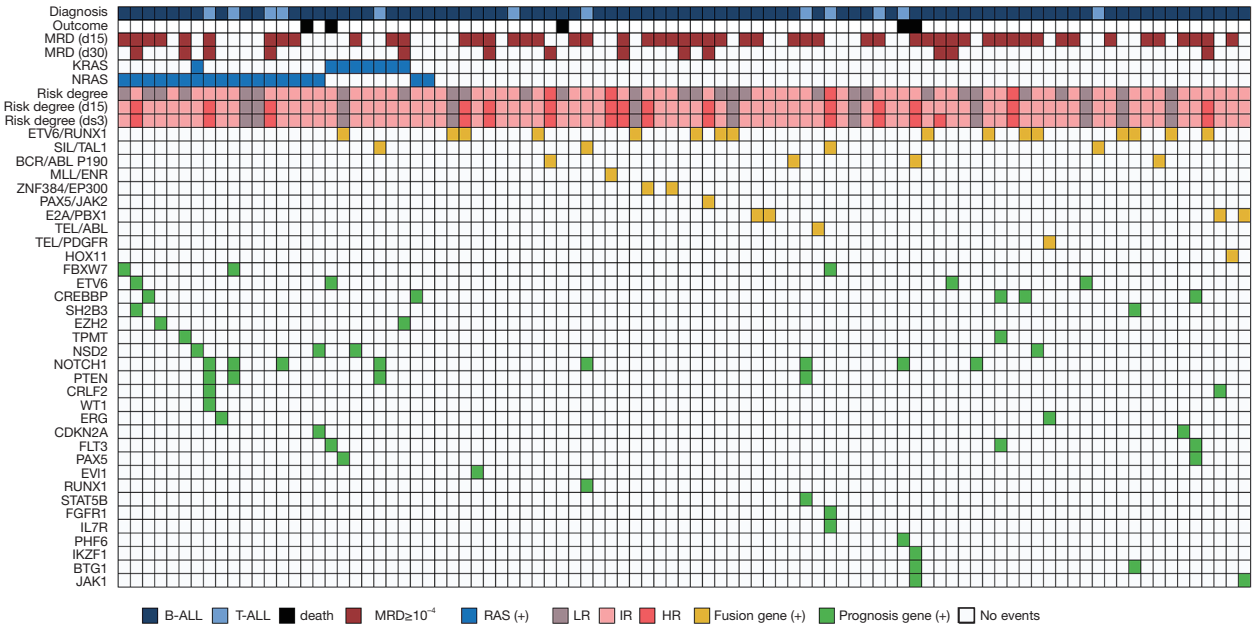

Figure 1 Heatmap of gene mutations in children with newly diagnosed ALL. MRD, minimal residual disease; *RAS*, rat sarcoma virus; LR, low risk; IR, intermediate risk; HR, high risk; ALL, acute lymphoblastic leukemia.

cancer, lung cancer, and other malignant tumors. In acute myeloid leukemia (AML), the *RAS* mutation is associated with hyperleukocytic leukemia, high lactate dehydrogenase (LDH) count and poor prognosis (21,22). Recent advances indicate that the *RAS* mutation also contributes to drug resistance in the treatment of AML (23). The relationship between *RAS* mutations and the prognosis of ALL remains unclear and controversial. This study analyzed the correlation between *RAS* gene mutations at initial diagnosis and adverse events during the first induction chemotherapy in 93 children with ALL and further evaluated new risk stratification and prognostic assessment indicators for pediatric ALL.

In this study, 19 cases of N-*RAS* mutation, 8 cases of K-*RAS* mutation, and 1 case of double mutation were detected in children with newly diagnosed ALL, with a detection rate of 26.9% (26/93). The *RAS* mutation rate in children with B-ALL was higher than that in children with T-ALL, which was basically consistent with the report by Wiemels *et al.* (24). Studies have reported that the *RAS* pathway can be used as a poor prognostic factor for B-ALL and that T-ALL with *RAS* pathway mutations are allergic to *MEK* inhibitor *in vitro* and *in vivo* (25). Huang *et al.* (26) analyzed bone marrow samples from 368 children newly diagnosed with Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-ALL), and found that *RAS* pathway mutation and *IKZF1* deletion were independent predictors of poor prognosis. The 10-year event-free survival (EFS; 11.1%±10.5%) and 10-year overall survival rate (53.3%±17.6%) of those with *IKZF1* deletion and *RAS* pathway mutation were the worst. In our study, only 2 children were detected with *IKZF1* deletion and negative *RAS* mutation. Considering the low sample size, we refrained from performing correlation analyses. Notably, this child eventually died due to severe infection.

All 93 children received induction chemotherapy under the CCLG-ALL 2018 protocol. Except for 5 children who died during induction period, all children completed induction chemotherapy. The 33-day bone marrow cell morphologically induced complete remission rate was 100%, and the 33-day MRD-negative conversion rate was 85.2% (75/88). The results show that the short-term efficacy of this regimen is excellent, which is similar to the clinical data of advanced pediatric hematology centers in Europe and America in recent years (27).

Studies have reported that hyperbilirubinemia during chemotherapy in ALL is mainly related to pegylated asparaginase (PEG-asparaginase) or asparaginase (28). Age >10 years was found to be a definitive risk factor for hyperbilirubinemia [odds ratio (OR) =3.83; 95% CI:

Table 3 Statistics of various adverse events during the first induction chemotherapy in children with ALL

Adverse events	*RAS* mutation (n=26)	*RAS* negative (n=67)	OR (95%)[1]	P value
Fever	35	50	0.95(0.22, 4.96)	0.947
Infection				N/A
At diagnose	12	29		
At induction	16	39		
Sepsis	5	17		N/A
Hypotension	2	4	4.48(0.34, 77.76)	0.253
Hypertension	0	1		N/A
Hypoxia	2	3		N/A
ARDS	2	3	4.48 (0.34, 77.76)	0.253
Pancreatitis	0	0		N/A
ALT elevation	13	19	0.80 (0.17, 3.75)	0.774
AST elevation	11	16	0.64 (0.13, 2.97)	0.57
Hyperbilirubinemia	0	7	0.03 (0, 0.39)	0.018*
Constipation	11	17	2.47 (0.88, 6.97)	0.085
ICU admission	1	5	2.08 (0.37, 10.97)[2]	0.381
Hyperglycemia	0	1	–[2]	N/A
TE	0	3	–	N/A
Stroke	0	0	–	N/A
Neuropathy	0	0	–	N/A
Seizure	0	0	–	N/A
Anaphylaxis	0	0	–	N/A
Hyponatrem	2	2	–	N/A
Ileus	1	1	–	N/A
Agranulocytosis duration (day)	18	24	–	N/A
Death	2	3	–	N/A

*, compared with the *RAS*-negative group, P<0.05; [1], model adjusted for age, sex, body mass index, infection status and antibiotic use; [2], the number of adverse outcomes during induction therapy was zero or too few to allow statistical analysis. ALL, acute lymphoblastic leukemia; ARDS, acute respiratory distress syndrome; ALT, alanine transaminase; AST, aspartate transaminase; TE, thromboembolism; ICU, intensive care unit; RAS, rat sarcoma virus; OR, odds ratio; N/A, not applicable.

1.64–8.95] (29). In addition, asparaginase-related adverse reactions also include hypersensitivity reaction, venous thromboembolism, and pancreatitis. In an multicenter phase II trial (NCT01920737), investigators used pediatric ALL regimens to further assess the safety and efficacy of different doses of asparaginase in 39 adults aged 20 to 60 years (median 38 years) with newly diagnosed ALL or lymphoblastic lymphoma. The results showed that patients aged 40–60 years (n=18) had a significantly higher probability of developing grade 3–4 hyperbilirubinemia than did patients aged 18–39 years (n=21; 44% *vs.* 10%; P=0.025) (30). In the present clinical trial, according to different disease risk and prognostic factors, anti-infection and supportive therapeutic strategies are adjusted in a timely manner, aiming to lower the incidence of adverse events occurring during the first induction chemotherapy for childhood ALL. Due to the small sample size, our study failed to further explore the related mechanism between

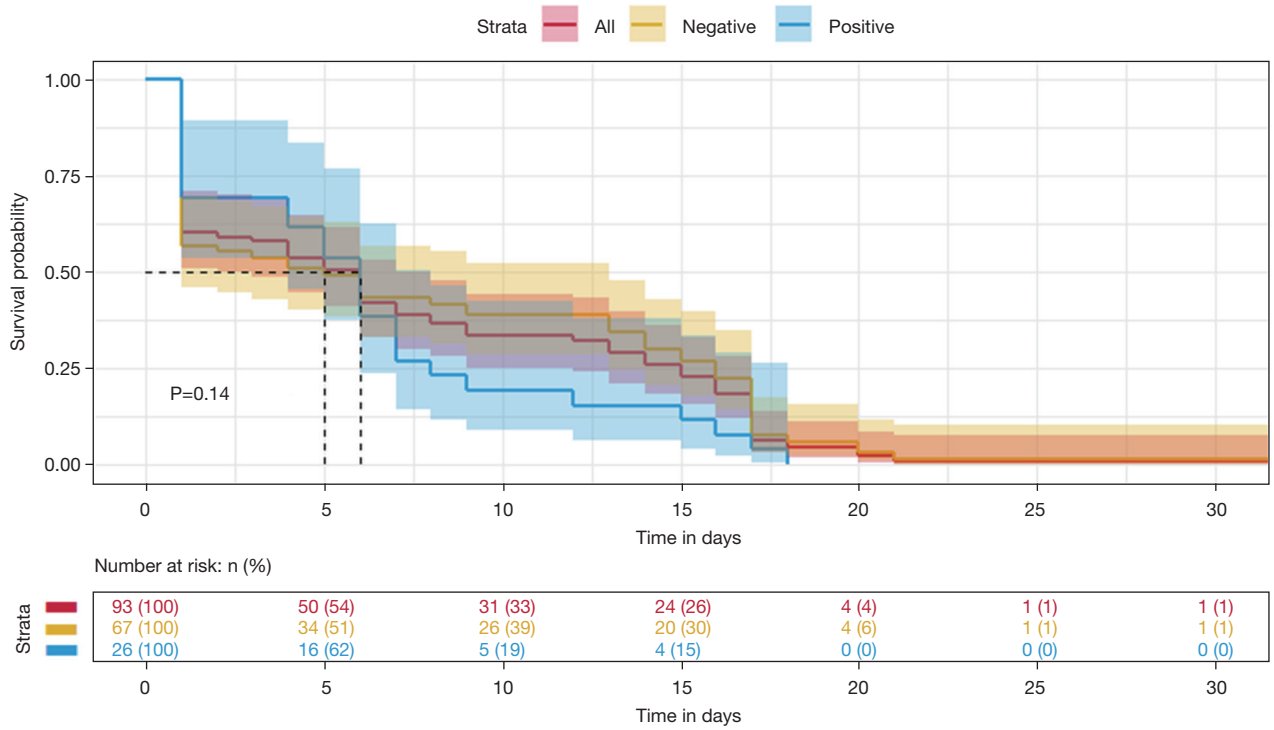

Figure 2 Survival function of occurrence and duration of agranulocytosis during the first chemotherapy in children with ALL. ALL, acute lymphoblastic leukemia.

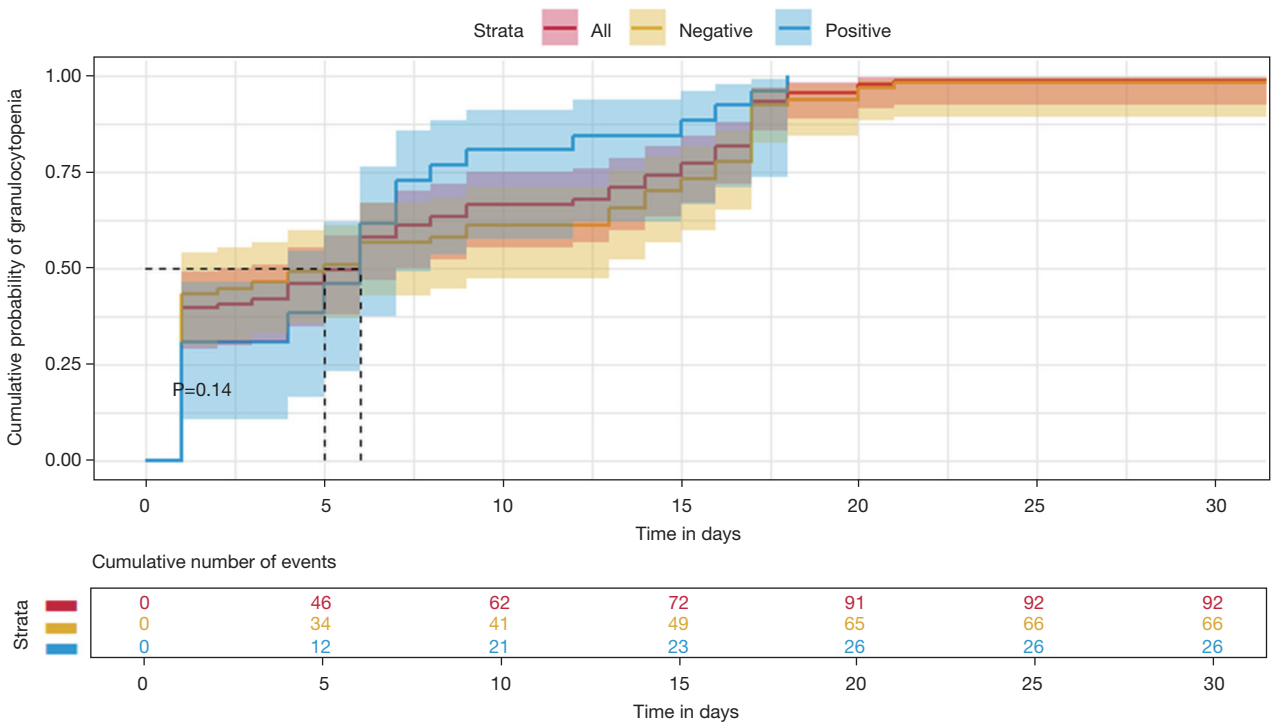

Figure 3 Risk function of occurrence and duration of agranulocytosis during the first chemotherapy in children with ALL. ALL, acute lymphoblastic leukemia.

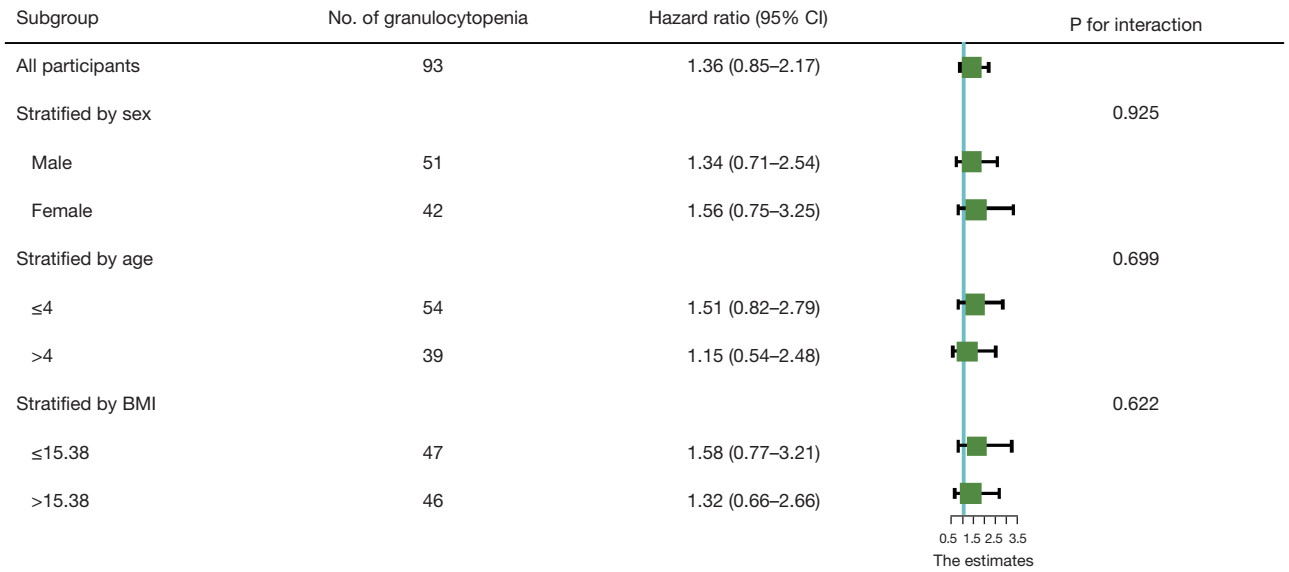

Figure 4 Cox proportional hazards model analysis for the effect of *RAS* gene mutations on the duration of agranulocytosis in children with ALL. BMI, body mass index; CI, confidence interval; *RAS*, rat sarcoma virus; ALL, acute lymphoblastic leukemia.

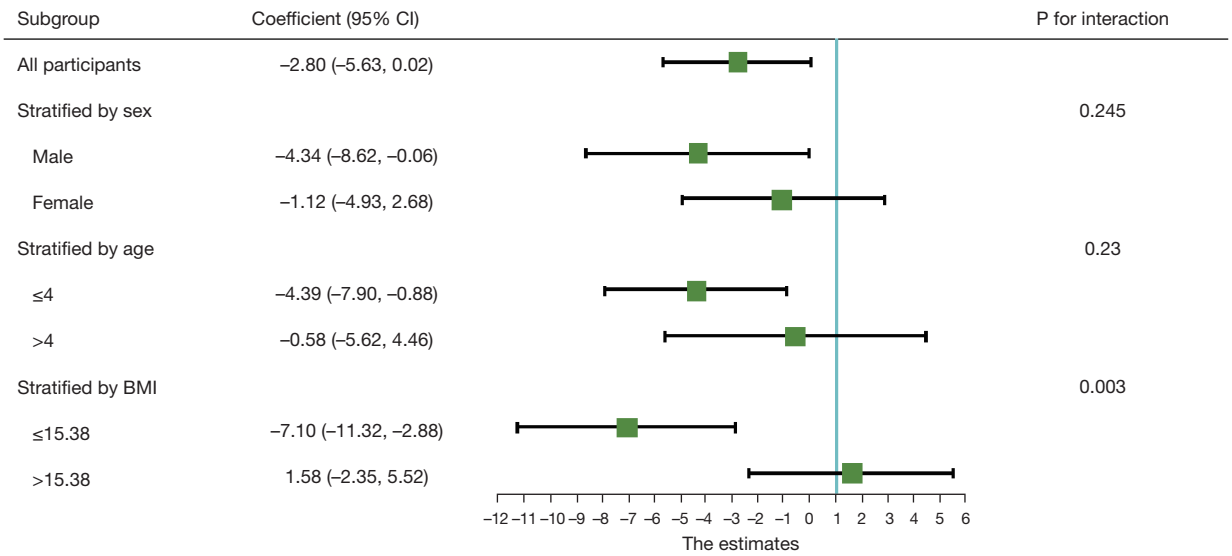

Figure 5 Multiple linear regression analysis for the effect of *RAS* gene mutation on the duration of agranulocytosis in children with ALL. BMI, body mass index; CI, confidence interval; *RAS*, rat sarcoma virus; ALL, acute lymphoblastic leukemia.

age and hyperbilirubinemia, and the occurrence of some specific CTCAE grade 2 or above adverse events with clinical significance in pediatric ALL was too low to be included in the statistical analysis. The sample size needs to be expanded in subsequent studies for further investigation.

In this study, multivariate analysis showed that, the risk of prolonged agranulocytosis was significantly increased in *RAS* mutation-positive group, when the BMI exceeded the median value of the study population (BMI >15.38; P=0.003). This may be due to the higher body fat percentage and lower systemic drug clearance rate in children with increased BMI. Chemotherapy drugs such as anthracyclines have a longer half-life, leading to prolonged agranulocytosis. According to the study by Sun *et al.* (31),

compared with that in a normal BMI group, the MRD of children with abnormally elevated BMI on day 19 and day 46 was higher (P=0.04 and P=0.008), and there was a positive correlation (P=0.014). Leptin resistance should be considered in children with high BMI. Recent studies also reported obesity to be a risk factor for chemotherapy-related osteonecrosis in children with ALL (OR =2.10, 95% CI: 1.12–3.95; P=0.02) (32). However, in another cohort study of Hispanic children with ALL, researchers found there to be no statistically significant difference in the disease-free survival (DFS) and OS rates between the overweight and obese group and the normal-weight group (33). Although the risk of overweight or obese status in more common in ALL/LL survivors than in survivors of other tumor types (67% *vs.* 14%; P=0.037), a series of future studies are needed to determine whether abnormally increased BMI is clearly associated with the prognosis of children (34).

Conclusion

In conclusion, this study showed that children with newly diagnosed ALL and *RAS* gene mutations were less likely to have fusion gene expression. *RAS* gene mutation increases the risk of prolonged agranulocytosis during the first induction chemotherapy and reduces the risk of hyperbilirubinemia in children with ALL. Due to limitations in the sample size and follow-up time, the possible influence of the *RAS* gene on various adverse events and long-term prognosis during the first induction chemotherapy of ALL needs to be further studied with a greater number of cases.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist Available at https://tp.amegroups.com/article/view/10.21037/tp-22-683/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-683/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-683/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Informed consent was obtained from patient's parents. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocols were approved by the Ethics Committee of Anhui Provincial Children's Hospital (No. CR20221210).

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