

# Asparaginase-associated pancreatitis during therapy for pediatric acute lymphoblastic leukemia

## Authors

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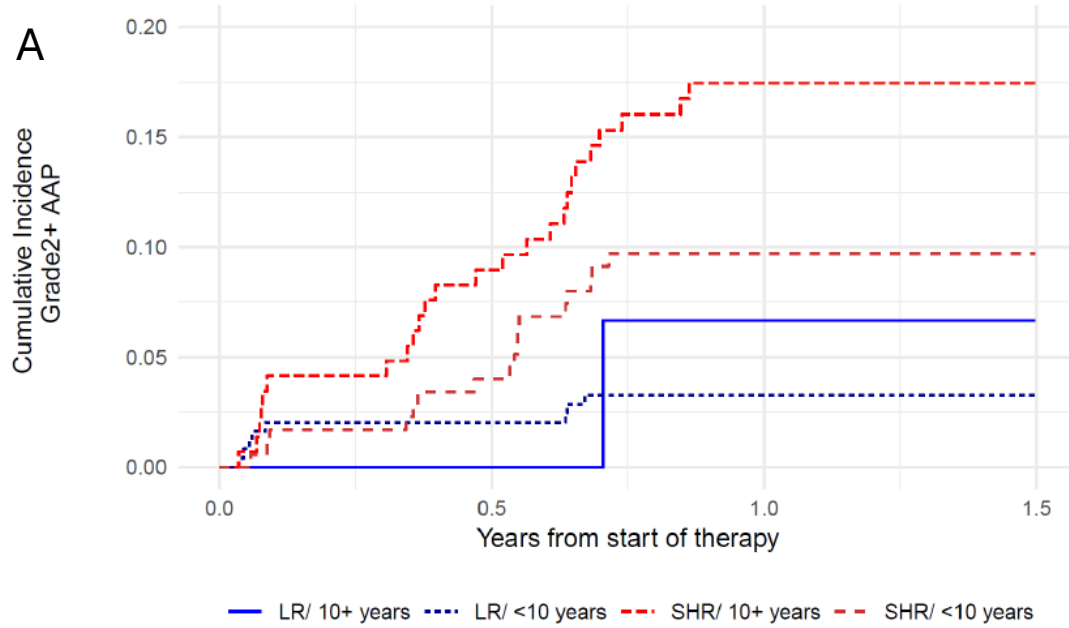
## Supplementary material

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Supplementary Figure 1: Pancreatitis incidence in Total 16 differed by age, treatment, and patient ancestry. (A) The 3-year cumulative incidence of pancreatitis was 4.5% in patients <10 years old receiving low-risk (LR) therapy, 8.9% in patients <10 years old receiving standard- or high-risk (SHR) therapy, 6.7% in older patients (10+) receiving low-risk therapy, and 18.9% in older patients receiving standard- or high-risk therapy. (B) The 3-year cumulative incidence of pancreatitis was 6.6% in European ancestry patients, 0% in Asian ancestry patients, 12.4% in African ancestry patients, 21.9% in Hispanic ancestry patients, and 13.2% in patients of other or mixed ancestry groups. Note that the Y-axis of both figures runs from 0-20%.

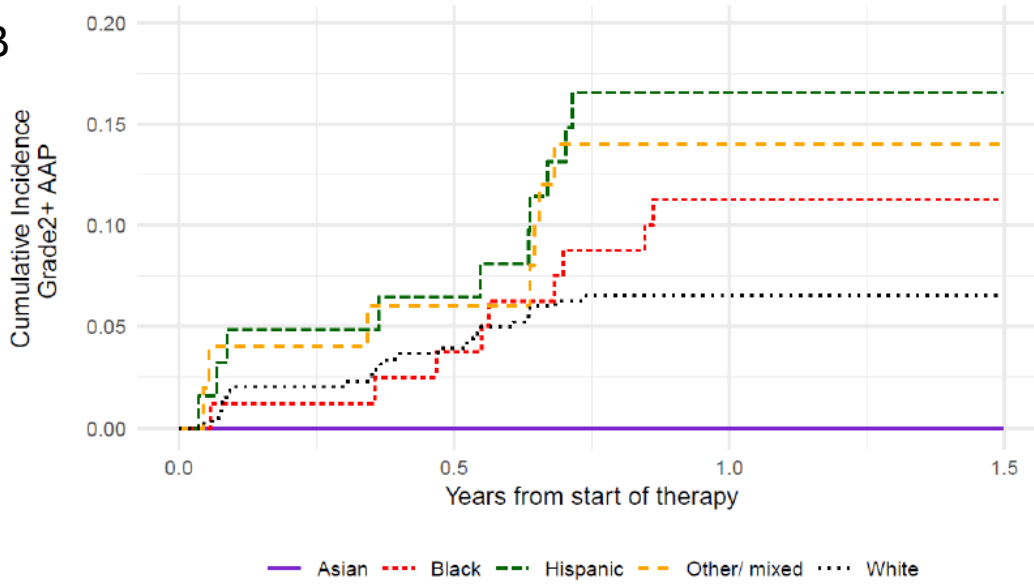
A



At Risk (Interval Events)

|                |         |          |          |         |
|----------------|---------|----------|----------|---------|
| LR/ 10+ years  | 15 (0)  | 15 (0)   | 14 (1)   | 14 (0)  |
| LR/ <10 years  | 245 (0) | 239 (5)  | 236 (3)  | 234 (0) |
| SHR/ 10+ years | 148 (0) | 132 (13) | 115 (12) | 112 (0) |
| SHR/ <10 years | 178 (0) | 168 (7)  | 154 (10) | 149 (0) |

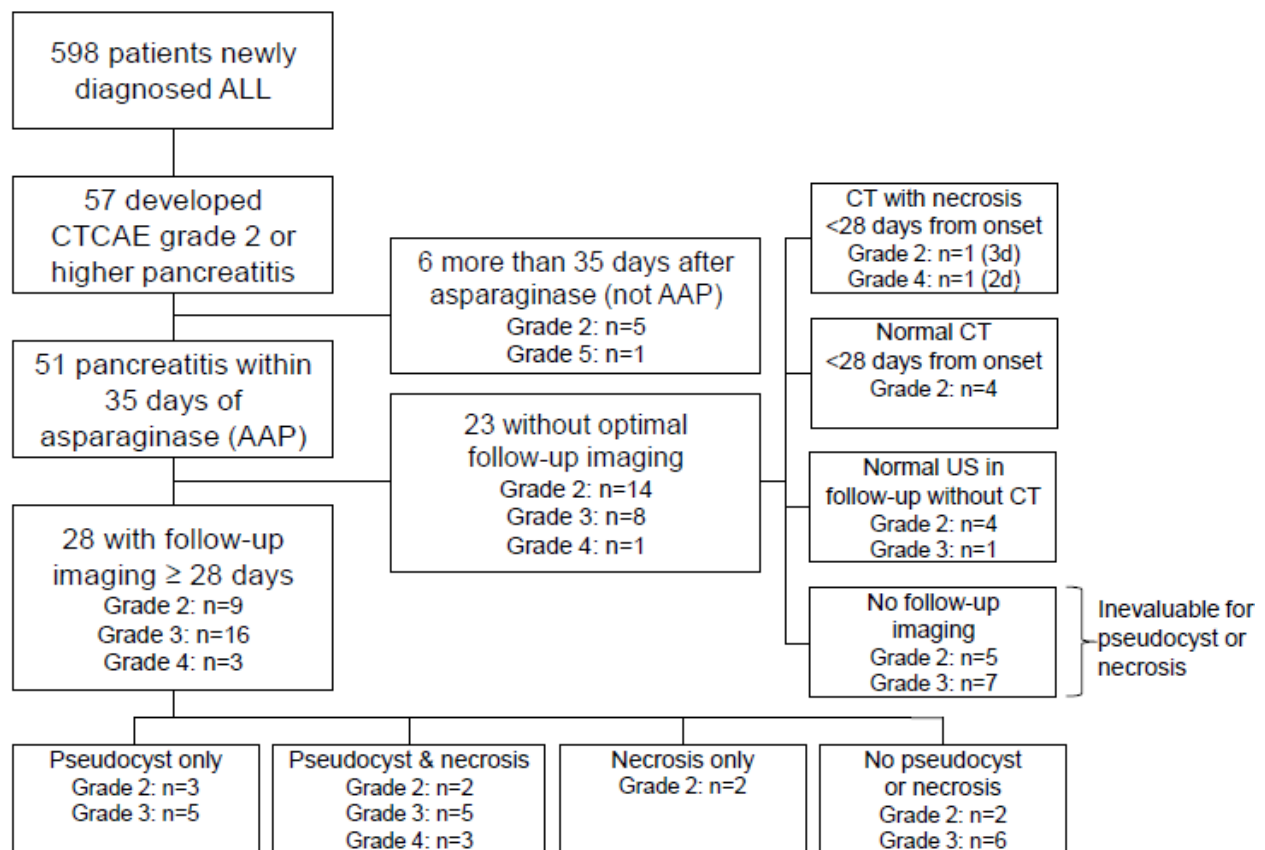
B



At Risk (Interval Events)

|              |         |          |          |         |
|--------------|---------|----------|----------|---------|
| Asian        | 4 (0)   | 4 (0)    | 4 (0)    | 4 (0)   |
| Black        | 81 (0)  | 77 (3)   | 70 (6)   | 67 (0)  |
| Hispanic     | 62 (0)  | 58 (4)   | 49 (6)   | 48 (0)  |
| Other/ mixed | 50 (0)  | 47 (3)   | 42 (4)   | 40 (0)  |
| White        | 387 (0) | 368 (15) | 354 (10) | 350 (0) |

Supplementary Figure 2: Among 51 patients with asparaginase associated pancreatitis, 39 had follow-up imaging after their initial diagnostic imaging. Pancreatic necrosis or pseudocyst occurred in 20/28 patients with imaging available at least 4 weeks after the onset of pancreatitis. Although imaging 28-90 days after the onset of AAP was preferred to define necrosis or pseudocyst, patients with evidence of necrosis prior to day 28 were considered to have had necrosis unless imaging was available after day 28 demonstrating complete resolution as this finding does not typically resolve.



Supplemental Table 1: Characteristics of patients with asparaginase associated pancreatitis (AAP)

| N  | Sex | Age at diagnosis (years) | IP | Risk group | Weight Category | BMI centile at dx | Genetic Ancestry | CTCAE v3.2 Grade | Pseudocyst or Necrosis | Prolong enzymes | AAP was severe | Hospital days | TPN days | ICU days | Total episodes | Recur was AAP | ASP prior to AAP | ASP after first AAP | ASP missed | Outcome            |
|----|-----|--------------------------|----|------------|-----------------|-------------------|------------------|------------------|------------------------|-----------------|----------------|---------------|----------|----------|----------------|---------------|------------------|---------------------|------------|--------------------|
| 1  | F   | 2.5                      | B  | SH         | Healthy         | 0.637             | Black            | 2                | NA                     | TRUE            | TRUE           | 9             | 22       | NA       | 1              | NA            | 6                | 1                   | 9          | HEM                |
| 2  | M   | 3.7                      | B  | SH         | Healthy         | 0.574             | White            | 2                | NA                     | FALSE           | FALSE          | 20            | 11       | NA       | 3              | (2/2)         | 1                | 7                   | 8          | CR                 |
| 3  | M   | 17.9                     | T  | SH         | Healthy         | 0.693             | White            | 2                | both                   | TRUE            | TRUE           | 11            | 7        | NA       | 2              | (1/1)         | 2                | 3                   | 11         | CNS                |
| 4  | M   | 9.9                      | B  | SH         | Overweight      | 0.884             | Black            | 3                | both                   | TRUE            | TRUE           | 4             | 15       | NA       | 1              | NA            | 3                | 0                   | 13         | HEM                |
| 5  | M   | 13.4                     | T  | SH         | Obese           | 0.985             | Black            | 3                | both                   | FALSE           | TRUE           | 9             | 26       | NA       | 1              | NA            | 8                | 0                   | 8          | CR                 |
| 6  | M   | 11.3                     | B  | SH         | Healthy         | 0.762             | Other            | 3                | NA                     | FALSE           | FALSE          | 11            | 15       | NA       | 1              | NA            | 9                | 0                   | 7          | CR                 |
| 7  | F   | 16.7                     | B  | Low (DS)   | NULL            | NULL              | Hispanic         | 3                | NA                     | NA              | FALSE          | 11            | 10       | NA       | 1              | NA            | 3                | 0                   | 2          | CR                 |
| 8  | M   | 13.4                     | B  | SH         | Obese           | 0.989             | Hispanic         | 3                | NA                     | FALSE           | FALSE          | 8             | 6        | NA       | 1              | NA            | 11               | 0                   | 5          | CR                 |
| 9  | F   | 4.3                      | B  | Low        | Healthy         | 0.072             | Other            | 2                | NA                     | TRUE            | TRUE           | NA            | NA       | 5        | 1              | NA            | 1                | 0                   | 4          | DIED INDUCTION     |
| 10 | F   | 3.2                      | B  | SH         | Healthy         | 0.590             | Hispanic         | 2                | necrosis               | NA              | TRUE           | 11            | 4        | 6        | 1              | NA            | 3                | 0                   | 13         | CR                 |
| 11 | F   | 12.9                     | B  | SH         | Healthy         | 0.412             | White            | 4                | both                   | TRUE            | TRUE           | 27            | 54       | NA       | 2              | (0/1)         | 2                | 0                   | 15         | CR                 |
| 12 | F   | 10.8                     | T  | SH         | Healthy         | 0.822             | White            | 3                | pseudocyst             | TRUE            | TRUE           | 70            | 25       | NA       | 1              | NA            | 10               | 0                   | 6          | CR                 |
| 13 | F   | 12.3                     | B  | SH         | Obese           | 0.996             | White            | 2                | NA                     | FALSE           | FALSE          | 5             | NA       | NA       | 2              | (1/1)         | 4                | 2                   | 10         | CR                 |
| 14 | M   | 11.4                     | B  | SH         | Obese           | 0.979             | White            | 3                | NA                     | TRUE            | TRUE           | 14            | NA       | NA       | 2              | (0/1)         | 10               | 0                   | 6          | CR                 |
| 15 | F   | 16.8                     | B  | SH         | Healthy         | 0.445             | White            | 3                | pseudocyst             | FALSE           | TRUE           | 10            | 25       | 5        | 1              | NA            | 2                | 0                   | 14         | CR                 |
| 16 | M   | 13                       | T  | SH         | Healthy         | 0.581             | White            | 4                | both                   | TRUE            | TRUE           | NA            | 153      | 9        | 1              | NA            | 8                | 0                   | 8          | CR                 |
| 17 | M   | 3.8                      | B  | SH         | Healthy         | 0.821             | White            | 3                | NA                     | FALSE           | FALSE          | 17            | 4        | NA       | 1              | NA            | 8                | 0                   | 8          | CR                 |
| 18 | F   | 6.2                      | B  | SH         | Healthy         | 0.447             | White            | 2                | NA                     | FALSE           | FALSE          | 6             | 115      | NA       | 1              | NA            | 4                | 12                  | 0          | HEM                |
| 19 | F   | 7.6                      | B  | Low        | Overweight      | 0.924             | White            | 4                | both                   | TRUE            | TRUE           | 23            | 56       | NA       | 1              | NA            | 5                | 0                   | 0          | CR                 |
| 20 | M   | 6.4                      | T  | SH         | Healthy         | 0.336             | White            | 3                | pseudocyst             | TRUE            | TRUE           | 11            | 67       | NA       | 1              | NA            | 7                | 0                   | 9          | CR                 |
| 21 | M   | 14.9                     | B  | SH         | Healthy         | 0.730             | Hispanic         | 2                | NA                     | FALSE           | FALSE          | 7             | NA       | NA       | 4              | (2/3)         | 1                | 6                   | 9          | CR                 |
| 22 | M   | 18                       | B  | SH         | Healthy         | 0.251             | White            | 3                | both                   | TRUE            | TRUE           | 23            | 35       | 3        | 1              | NA            | 2                | 0                   | 14         | CNS                |
| 23 | M   | 1.9                      | T  | SH         | NULL            | NULL              | Black            | 2                | NA                     | FALSE           | FALSE          | 5             | NA       | NA       | 2              | (1/1)         | 2                | 4                   | 10         | CR                 |
| 24 | M   | 9.3                      | T  | SH         | Obese           | 0.996             | Other            | 3                | pseudocyst             | TRUE            | TRUE           | 12            | 7        | NA       | 1              | NA            | 3                | 0                   | 13         | CR                 |
| 25 | M   | 9.9                      | B  | SH         | Healthy         | 0.402             | White            | 3                | NA                     | TRUE            | TRUE           | 9             | NA       | NA       | 1              | NA            | 11               | 0                   | 5          | HEM                |
| 26 | F   | 14.9                     | B  | SH         | Obese           | 0.980             | Black            | 3                | NA                     | NA              | FALSE          | 3             | NA       | NA       | 1              | NA            | 14               | 0                   | 2          | CR                 |
| 27 | M   | 12.8                     | T  | SH         | Healthy         | 0.226             | Other            | 2                | NA                     | FALSE           | FALSE          | 3             | NA       | NA       | 2              | (1/1)         | 11               | 5                   | 0          | CR                 |
| 28 | M   | 2.2                      | B  | SH         | Healthy         | 0.739             | White            | 2                | NA                     | FALSE           | FALSE          | 14            | NA       | 7        | 4              | (1/3)         | 1                | 3                   | 12         | CR                 |
| 29 | F   | 9                        | T  | SH         | Overweight      | 0.885             | Other            | 3                | NA                     | FALSE           | FALSE          | 2             | NA       | NA       | 1              | NA            | 10               | 0                   | 6          | CR                 |
| 30 | M   | 7.8                      | B  | SH         | Obese           | 0.978             | Hispanic         | 3                | both                   | FALSE           | TRUE           | 10            | 63       | NA       | 1              | NA            | 10               | 0                   | 6          | CR                 |
| 31 | M   | 13.4                     | T  | SH         | Obese           | 0.961             | White            | 2                | necrosis               | FALSE           | TRUE           | 5             | NA       | NA       | 3              | (1/2)         | 3                | 1                   | 12         | CR                 |
| 32 | M   | 6.8                      | B  | Low        | Healthy         | 0.256             | White            | 4                | necrosis               | TRUE            | TRUE           | 16            | 12       | 8        | 1              | NA            | 1                | 0                   | 4          | CR                 |
| 33 | M   | 16.9                     | B  | SH         | Healthy         | 0.123             | White            | 2                | NA                     | FALSE           | FALSE          | 6             | 3        | NA       | 1              | NA            | 1                | 15                  | 0          | CR                 |
| 34 | M   | 14.6                     | B  | SH         | Healthy         | 0.733             | White            | 3                | pseudocyst             | TRUE            | TRUE           | 49            | NA       | 1        | 1              | NA            | 11               | 0                   | 5          | CR                 |
| 35 | M   | 11.5                     | B  | SH         | Healthy         | 0.166             | Black            | 3                | NA                     | FALSE           | FALSE          | 11            | NA       | NA       | 1              | NA            | 11               | 0                   | 5          | CR                 |
| 36 | M   | 9.3                      | T  | SH         | Obese           | 0.991             | Black            | 2                | both                   | TRUE            | TRUE           | 10            | NA       | NA       | 2              | (0/1)         | 1                | 0                   | 15         | CR                 |
| 37 | M   | 5.7                      | B  | Low        | Overweight      | 0.918             | Hispanic         | 2                | pseudocyst             | TRUE            | TRUE           | 4             | 84       | NA       | 1              | NA            | 5                | 0                   | 0          | CR                 |
| 38 | M   | 5.2                      | B  | Low        | Overweight      | 0.855             | White            | 2                | pseudocyst             | FALSE           | TRUE           | 6             | 102      | 4        | 1              | NA            | 1                | 0                   | 4          | CR                 |
| 39 | M   | 18.5                     | B  | SH         | Obese           | 0.987             | Black            | 2                | NA                     | NA              | FALSE          | 15            | 23       | NA       | 1              | NA            | 16               | 0                   | 0          | CNS                |
| 40 | M   | 10.1                     | T  | SH         | Healthy         | 0.106             | White            | 2                | NA                     | TRUE            | TRUE           | 15            | NA       | NA       | 2              | (1/1)         | 4                | 10                  | 2          | CR                 |
| 41 | M   | 10.3                     | T  | SH         | Healthy         | 0.788             | White            | 2                | NA                     | FALSE           | FALSE          | 4             | NA       | NA       | 1              | NA            | 1                | 15                  | 0          | CR                 |
| 42 | F   | 7.6                      | B  | Low        | Healthy         | 0.571             | Other            | 2                | NA                     | FALSE           | FALSE          | 11            | NA       | NA       | 2              | (1/1)         | 1                | 2                   | 2          | CR                 |
| 43 | M   | 12.5                     | B  | SH         | Healthy         | 0.842             | Hispanic         | 2                | NA                     | FALSE           | FALSE          | 8             | NA       | NA       | 2              | (1/1)         | 1                | 12                  | 3          | CR                 |
| 44 | M   | 2.8                      | B  | SH         | Obese           | 0.961             | Hispanic         | 2                | necrosis               | FALSE           | TRUE           | 2             | NA       | NA       | 4              | (0/3)         | 11               | 0                   | 5          | CR                 |
| 45 | F   | 8                        | B  | SH         | Obese           | 0.996             | Hispanic         | 3                | NA                     | FALSE           | FALSE          | 4             | NA       | NA       | 1              | NA            | 8                | 0                   | 8          | CR                 |
| 46 | M   | 11.6                     | T  | SH         | Overweight      | 0.937             | Black            | 2                | NA                     | TRUE            | TRUE           | 4             | NA       | NA       | 1              | NA            | 11               | 0                   | 5          | DIEDCR             |
| 47 | F   | 5.7                      | B  | Low        | Overweight      | 0.901             | White            | 2                | NA                     | TRUE            | TRUE           | 15            | 22       | NA       | 1              | NA            | 1                | 0                   | 4          | CR                 |
| 48 | M   | 2                        | B  | SH         | Healthy         | 0.729             | Other            | 2                | NA                     | TRUE            | TRUE           | 17            | NA       | NA       | 1              | NA            | 11               | 0                   | 5          | CR                 |
| 49 | F   | 13.8                     | B  | SH         | Overweight      | 0.859             | Hispanic         | 2                | NA                     | FALSE           | FALSE          | 6             | NA       | NA       | 1              | NA            | 1                | 5                   | 10         | CR                 |
| 50 | M   | 14.2                     | B  | SH         | Healthy         | 0.563             | White            | 3                | both                   | FALSE           | TRUE           | 10            | 52       | 5        | 1              | NA            | 2                | 0                   | 14         | Primary refractory |
| 51 | F   | 6.8                      | B  | Low        | Healthy         | 0.461             | White            | 2                | pseudocyst             | TRUE            | TRUE           | 9             | NA       | 3        | 2              | (0/1)         | 5                | 0                   | 0          | CR                 |

IP: immunophenotype; SH: standard/high risk; DS: Down Syndrome; AAP: pancreatitis within 35 days of asparaginase; prolong enzymes: amylase or lipase ≥3x the upper limit of lab normal at 72 hours; severe AAP had either pseudocyst, necrosis, or prolonged enzyme elevation; TPN: total parenteral nutrition; ICU: intensive care unit; Recur was AAP shows the number of recurrent episodes of AAP and the total episodes of recurrent pancreatitis; ASP: asparaginase doses measured as either 1 dose of PEGaspargase or the equivalent doses of Erwinia derived asparaginase; HEM: bone marrow relapse; CNS: CNS relapse; CR: ongoing complete remission