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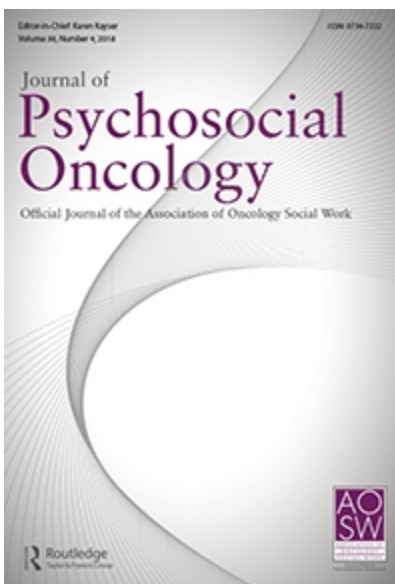
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Screening for distress in pediatric cancer survivors: A systematic comparison of one-step and two-step strategies to minimize detection errors

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3 **Screening for distress in pediatric cancer survivors: A systematic comparison of**
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5 **one-step and two-step strategies to minimize detection errors.**
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10 **Abstract**

11 **Background.** Childhood cancer survivors should be routinely screened for
12 psychological distress. However, existing screening tools promoted by cancer care
13 institutions, such as the Distress Thermometer (DT) generate high rates of errors. The aim
14 of this study is to help refining strategies of screening psychological distress in this
15 population by exploring two-step methods combining the DT on step #1 with one question
16 on step #2. **Procedure.** Data from 255 survivors of childhood acute lymphoblastic leukemia
17 aged 13-40 years were analyzed (38% 13-18 years, 62% 19+ years, 53% females). We used
18 the DT on step #1 and the individual emotion items from the Pediatric Quality of Life
19 Questionnaire (PedsQL) on step #2, to detect distress, depression and anxiety as measured
20 by standard instruments. We compared sensibility, specificity, negative and positive
21 predictive values, Youden index, and clinical utility indices, in newly developed two-step
22 strategies. **Results.** The best two-step strategies to screen anxious-depressive distress were
23 DT ≥ 2 on step #1, with the item of Sadness on step #2, and DT ≥ 2 combined with the
24 item of Concerns. Two-step strategies outperformed the DT alone on the correct
25 identification of distressed survivors. However, two-step strategies did not outperform the
26 DT used alone on the correct detection of no distressed survivors. Results were similar
27 when predicting depression or anxiety alone. **Conclusion.** Completing the DT with one
28 single question on emotions from the PedsQL may minimize the number of participants
29 falsely identified as distressed, which could be particularly pertinent in resource-limited
30 clinics.
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5 **Keywords:** Screening, emotional distress, depression, anxiety, pediatric cancer, survivors
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For Peer Review Only

Introduction

Large studies like the Childhood Cancer Survivors Study (CCSS) and the St-Jude Lifetime cohort (SJLT) have demonstrated that pediatric cancer survivors were at higher risk of depression, anxiety, behavioral difficulties, distress, as well as post-traumatic symptoms, when compared to siblings or other normative samples.¹⁻⁷ Longitudinal follow-ups have also found that distress frequency evolves over time, with more than 10% of survivors experiencing significant increase in depression and anxiety.⁸ The development of late effects seem to play a core role in the long-term psychological status of survivors.^{5,8-11} This emphasizes the necessary regular monitoring of emotional distress in survivors, as promoted by leading cancer agencies. The National Comprehensive Cancer Network (NCCN) defines distress as a “multifactorial unpleasant emotional experience of a psychological (i.e. cognitive, behavioral, emotional), social, spiritual, and/or physical nature”.¹²

As numbers of pediatric cancer survivors have increased dramatically, professionals are searching optimal ways to care for this growing vulnerable population and accurately identify emotional distress.¹²⁻¹⁶ Indeed, aftercare clinics are facing a major challenge regarding the optimal allocation of their limited resources for psychosocial assessment and services.^{15,17-19} One of the approaches taken to better serve this population while optimizing resource allocation is to regularly screen individuals at-risk for psychological difficulties.²⁰⁻²³ Because they are far more acceptable, easy to use by non-specialists, and may be taken repetitively along the cancer trajectory, cancer agencies have recommended ultra-short tools, typically consisting of one or two-item instruments.²⁴ Several tools have been used with pediatric cancer survivors.^{15,25-27} Among these, the ultra-short Distress

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3 Thermometer (DT) is a single-item self-report tool for identifying psychological distress
4 on a 10-point scale (0 = no distress to 10 = extreme distress).²⁸⁻³² The DT is now largely
5 used in adult oncology,³³⁻⁴² and in pediatric survivors.²⁸⁻³⁰ It is one of the recommended
6 tools for monitoring distress across cancer care centers in some provinces of Canada,
7 including Quebec.⁴³ Available data in pediatric cancer survivors suggest the DT is accurate
8 when it comes to identifying patients or survivors with no emotional distress. For cut-points
9 of 1+ or 2+, it yielded Negative Predictive Values (NPV) of 97-94% and specificities (Sp)
10 of 51-69%.⁴⁴ This is consistent with cumulative evidence showing that this tool had good
11 accuracy of a negative screen, comparable to longer tools.^{45,46} However, research has
12 suggested that such an ultra-short screening tool may not be sufficient to warrant referral
13 on its own, because of the high rate of false positives (FP).⁴⁷

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15 To deal with this difficulty in settings where ultra-short tools are being considered,
16 a second step will be needed in those who screen positively as possible cases.^{33,48,49} There
17 are strong methodological arguments in favor of a sequential approach when identifying
18 cases since case identification functions better when base rate is closer to 50%.^{50,51} The
19 first step would use a test with a high sensitivity at a cut-point to ensure that very few cases
20 are missed, even though this results in a large number of FP. The second step would use a
21 test with a high specificity and a cut-point which discard the most FP to perform better.⁵⁰
22 So far, few studies have compared screening tools head to head for their ability to detect
23 distress in cancer care yet, and no studies have done so pediatric cancer survivors.⁵²

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25 The objective of this study was to develop a simple strategy to detect significant
26 psychological distress, depression, and anxiety in survivors of pediatric cancer, based on a
27 combination of widely used existing ultra-short tools and items. Specific objectives were:
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3 (1) To develop optimal detection strategies to identify cases with significant distress,
4 depression and anxiety. Based on previous research, we articulated two steps: (a) optimally
5 rule-out survivors *without* distress (i.e. identification of non-cases), (b) in the remaining
6 sub-sample, optimally rule-in survivors *with* distress (i.e. case identification); (2) to
7 compare performances of these strategies with the use of the DT alone at pre-established
8 cut-points.
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16 **Methods**

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19 **Study design.** This study consists in an analysis of cross-sectional data collected
20 by two Canadian treatment centers in leukemia survivors: the Sainte-Justine University
21 Health Center (SJUHC, Montreal, n=218) and the Laval University Health Center (CHUL,
22 Quebec, n=37). As part of cohort biomarkers follow-ups, we have been collecting detailed
23 psychological description in survivors of pediatric ALL to describe their current status.⁵³
24 The present study assessed alternative strategies to accurately identify cases of distress,
25 depression and anxiety.
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35 **Sample.** The study sample includes 255 pediatric cancer survivors (n=98; 38%
36 adolescents, 13-18 years; n=157; 62% adults >18 years; 47% males; 53% females) treated
37 for childhood acute lymphoblastic leukemia (ALL) with the Dana Farber Cancer Institute
38 (DFCI) protocols since 1989, being at least 5 years from diagnostic with no recurrence.
39 These childhood cancer survivors were recruited from the PETALE cohort and the PSY-
40 ALL project, between February 2013 to May 2016. The sample of the present study
41 represents about 56% (n=255) of the total childhood ALL patients treated in the two centers
42 at the recall date (supporting Information Figure S1). Table 1 presents the
43 sociodemographic and treatment characteristics of the sample.
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3 **Measures.** We collected standard sociodemographic data with a self-report
4 questionnaire and clinical history was collected from the medical files. The psychosocial
5 status was evaluated with standardized self-report instruments widely used to derive rates
6 of distress in this population and with good concordance with a psychiatric interview.⁵⁴⁻⁵⁶
7 Reference instruments used to evaluate mixed distress (depression and/or anxiety),
8 depression and anxiety, were the *Brief Symptom Inventory-18* (BSI-18), administered for
9 participants aged >18 years,⁵⁷ and the *Beck Youth Inventory* depression and anxiety
10 modules (BYI-AD), administered for participants aged ≤18 years.⁵⁸ Internal consistency
11 reliability indices of the BSI-18 in this study were $\alpha=0.79$ (depression, 6 items) and $\alpha=0.79$
12 (anxiety, 6 items). The cut-point $T \geq 63$ was used to identify cases of mixed distress,
13 depression and anxiety among adults >18 years, according to the BSI-18 manual.⁵⁷ The
14 cut-point of $T \geq 60$ on the BYI-AD was used to identify cases of distress, depression and
15 anxiety among adolescents ≤18 years. This cut-point refers to moderate to severe
16 depression or anxiety on the BYI-AD.⁵⁸ Reliability indices of the BYI were: $\alpha=0.92$ and
17 0.91 for the depression and anxiety modules respectively (20 items each).

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38 The test measure at step #1 was the *Distress Thermometer* (DT, and the version for
39 youngsters: the *Distress Rating Scales*, DRS). These are single-item, self-report, visual
40 analogue scales with scores from 0 = no distress to 10 = extreme distress, to evaluate
41 distress in the past week.^{29,59} For step #2, we used the five individual items from the
42 emotional subscore of the *Pediatric Quality of Life Inventory Generic Scale* 4.0 version
43 (PedsQL 4.0, adolescent and adult versions). The items evaluate fear, sadness, anger, sleep
44 and concerns issues (Fear: “I feel afraid or scared”, Sadness: “I feel sad or blue”, Anger:
45 “I feel angry”, Sleep: “I have trouble sleeping”, Concern: “I worry about what will happen
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3 to me”).^{60,61} Each item is responded on a 0-4 scale (0 = never a problem, to 4 = almost
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5 always a problem). In the analyses, positivity was considered as a score of 2 or more, as
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7 very low base rates were observed for scores of 3 or 4 (median base rate 8.2%). The
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9 PedsQL was chosen for step #2 because it inquires specific complains, is available across
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11 ages and is routinely used with cancer survivors in cancer centers. In addition, its items are
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13 frequently available in existing databases, which will facilitate replication studies.
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17 **Analysis.** For objective 1, we computed Sensitivity (Se), Specificity (Sp), Positive
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19 predictive value (PPV), Negative predictive value (NPV), Youden Index ($J = \text{sensitivity} +$
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21 $\text{specificity} - 1$), Clinical Utility Indices (CUI+ and CUI-) to detect distress (depression
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23 and/or anxiety), depression, and anxiety on the BSI and BYI-AD.^{50,51,62-65} For consistency
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25 across ages, distress was defined as a presence of either depression, anxiety, or both. On
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27 step #1, we searched the most effective cut-point to detect distress, depression and anxiety
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29 on the DT, i.e. a cut-point maximizing specificity and NPV while minimizing cases of FN.
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31 We set a condition of a maximum of false negatives errors of $n=2$ for this step, as these
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33 errors are the most important in screening. Test negatives from step #1 were removed for
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35 step #2 analyses in order to increase base rates.^{50,63} Step #2 included a more balanced
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37 strategy to optimize case identification while not compromising too much on non-case
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39 identification. At step #2, we maximized the Youden Index, which gives equal importance
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41 to positive and negative misclassified results (false positives and false negatives), with
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43 minimal levels of sensibility and specificity of 0.50.⁶² Two-step strategies were then
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45 compared on their overall diagnostic performances as evaluated by Clinical Utility Indices
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47 (CUI).⁶³⁻⁶⁵ The negative clinical utility index (CUI- = $\text{specificity} \times \text{NPV}$) was used to
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49 compare strategies on their rule-out ability, while the positive clinical utility index (CUI+
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= sensitivity x PPV) was used to assess rule-in ability. For objective 2, the best two-step strategies selected were compared to the DT used alone (cut-points 4 and 5) on the CUI+ and the CUI- and their 95% CIs. We used the software IBM SPSS Statistics 25 for Windows for all analyses.

Results

Preliminary analysis. In the study sample of 255, 15% of survivors (95% CI=11-20%) reported significant levels of distress as measured on the BYI-AD and the BSI-18. Ten percent (95% CI=7-15%) reported significant levels on depression, and 9% (95% CI=6-14%) had significant levels on anxiety. Only 5% (95% CI=2-8%) had both depression and anxiety. When looking into test measures, 33% (95% CI=27-39%) had a DT score \geq 3, 23% (95% CI=18-28%) had a DT score \geq 4, and 17% (95% CI=13-22%) had a DT score \geq 5. On the PedsQL emotional items, we found significant levels on Fear (18%; 95% CI=14-23%), Sadness (33%; 95% CI=27-39%), Anger (33%; 95% CI=27-39%), Sleep (32%; 95% CI=27-38%), and Concerns (31%; 95% CI=26-37%).

Step #1 for distress. Figure 1 describes participants' responses on the DT according to their psychological distress status. Two alternate cut-points were appropriate. With DT \geq 1, 36% of the sample could be ruled out with no error of false negatives (NPV=100%). With DT \geq 2, 49% of the sample could be ruled out with 1 false negative error (NPV=99.2%). Although DT \geq 3 ruled out 65% of the sample, it also falsely identified 5 participants as negatives (NPV=97.1%), a number we judged unacceptable for screening purposes as we initially set a maximum of n=2 FN errors for this step. Consequently, only cut points of 1 and 2 on the DT were considered in further analyses.

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3 **Step #2 for distress.** On the subsample identified as positive following step #1, we
4 explored diagnostic performances (Specificity, Sensitivity, Youden Index J) of the five
5 emotional items from the PedsQL (Figure 2, and supporting information Figure S2), which
6 resulted in 10 exploratory configurations, i.e. two DT cut-points on step #1 x five PedsQL
7 items on step #2. The best strategies should have the higher Youden Index and a reasonable
8 balance of specificity and sensitivity, at best higher than 50%. On step #2, two questions
9 outperformed the others with specificity and sensitivity higher than 50% (63-82%) and
10 Youden Index (J) approaching 0.50: Concerns (J=0.49) and Sadness (J=0.48).
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13 **Selection of two-step strategies.** When comparing the ten two-step strategies on
14 their overall performances by means of their CUI, two strategies appeared to outperform
15 the others: (1) $DT \geq 2$ combined with Concerns (CUI-=-0.81; CUI+=0.37) and (2) $DT \geq 2$
16 combined with Sadness (CUI-=-0.81; CUI+=0.37) (Figure 2 and supporting information
17 Figure S2).
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20 **Comparison of the newly developed two-step strategies with the DT alone.** We
21 compared the two selected two-step strategies (Strategy 1: $DT \geq 2$ combined with Concerns;
22 Strategy 2: $DT \geq 2$ combined with Sadness) with the one-step strategy using the DT alone
23 at most popular cut-points of 4 and 5 (Table 2). When considering non-case identification,
24 both selected strategies had significantly lower ability than the $DT \geq 5$ alone (non-
25 overlapping 95% CIs), and similar ability as the $DT \geq 4$. Interestingly the two-step strategies
26 had significant higher case identification abilities than both $DT \geq 4$ and $DT \geq 5$.
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29 **Extension of results to the detection of depression and anxiety.** We applied the
30 same procedures to the detection of depression (Table 2 and supporting information
31 Figures S3 and S4) and anxiety separately (Table 2 and supporting information Figures S5
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3 and S6). For depression, the best two-steps strategies were: (1) $DT \geq 3$ combined with
4 Sadness and (2) $DT \geq 2$ combined with Sadness. Strategy 1 had significantly higher non-
5 case identification and case identification performances than the $DT \geq 4$ alone, and only
6 significantly higher case identification performance than the $DT \geq 5$. Strategy 2 had
7 significantly lower non-case identification ability than the $DT \geq 5$ alone, no significant
8 differences in non-case identification ability than the $DT \geq 4$, and no significant differences
9 in case identification ability than the $DT \geq 4$ and $DT \geq 5$.

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12 For anxiety, the best two-step strategies were (1) $DT \geq 2$ combined with Concerns
13 and (2) $DT \geq 1$ combined with Concerns. Strategy 1 had similar non-case identification
14 performance as the $DT \geq 4$, and a lower non-case identification performance than the $DT \geq 5$.
15 Strategy 1 showed a significant higher case identification performance than the $DT \geq 4$ and
16 $DT \geq 5$. Strategy 2 showed similar non-case identification ability as the $DT \geq 4$ and lower
17 non-case identification ability than the $DT \geq 5$. Strategy 2 outperformed significantly case
18 identification abilities of both $DT \geq 4$ and $DT \geq 5$.

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Discussion

The objectives of this study were to identify a two-step strategy to detect distress, depression, and anxiety, and compare its efficacy with the DT used alone. When comparing strategies face-to-face on their detection abilities, we found that combining a non-case identification step involving the $DT \geq 1$ or $DT \geq 2$, with a case identification step involving two emotional questions from the PedsQL (Sadness or Concerns) generally outperformed the use of the DT alone, specifically if using the cut-point $DT \geq 4$. Notably, two-step strategies were significantly better at detecting cases at-risk of distress, depression and

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3 anxiety. Yet, two-step strategies yielded similar non-case identification performances as
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5 the established cut-point of a $DT \geq 4$.
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8 A preliminary observation from the results suggests that the study sample showed
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10 similar rates of depression but lower rates of anxiety than what is observed in typically
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12 developing individuals. The NIMH has found rates of anxiety of up to 30% in adolescents
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14 and 19% in adults, in comparison to a 9% here. This suggests the participants to our study
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16 were in a good mental condition. As base rates are essential to compute reliable diagnostic
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18 indices, it is possible that this characteristic of the sample may limit the performances of
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20 the case detection step #2.⁶⁶
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24 These results suggest that two-step strategies composed of ultra-short items may
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26 significantly improve the identification of positive cases of distress, depression or anxiety
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28 over the usual one-step strategy recommended by cancer care national institutions.^{12,32,42,43}
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30 In our sample, the strategy combining $DT \geq 2$ with the Concerns item identified correctly
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32 $n=30$ participants with distress with distress, compared with the $n=27$ correctly identified
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34 when using the $DT \geq 4$ alone, and only $n=23$ identified with the $DT \geq 5$ alone. This pattern
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36 was observed for most two-step strategies tested. These two-step strategies yielded lower
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38 false positive rates than the DT used alone. Importantly, this gain was not made at the
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40 expense of false negatives. In our group, Strategies 1 ($DT \geq 2$ combined with Concerns) and
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42 2 ($DT \geq 2$ combined with Sadness) erroneously identified $n=8$ cases with distress as
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44 negatives whereas the figures were higher for the DT alone: $n=11$ for $DT \geq 4$, and $n=15$ for
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46 $DT \geq 5$. These results mean that if we were using the DT alone for screening and reference,
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48 3-7 additional participants would have missed the opportunity of further evaluation and
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3 follow-up, whereas these participants would have been identified with the present
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5 strategies.
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8 The results confirm the low ability of the ultra-short screening tools like the DT
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10 used alone to detect positive cases of distress, depression or anxiety.^{28,30,35,45,46,67} In contrast,
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12 ultra-short screening tools have been recognized for their high abilities to discard true
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14 negatives.^{28,30,35,46,68} In that regard, when using a low cut-point, the performances of the
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16 DT were almost perfect, but when used alone it was at the expense of a very high rate of
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18 false positives (False Discovery Rate or $FDR=1-PPV=0.77$ and 0.71 for $DT \geq 1$ and $DT \geq 2$
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20 respectively). Such rates are not acceptable in practice, as they would induce unbearable
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22 workload on the follow-up clinic. The interest of two-step strategies was well exemplified
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24 here, as the specific symptomatic or emotional items help reduce these errors.
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28 The results of the current study have important implications for screening
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30 psychological distress in the long-term follow-up clinic. First, the capacity of a two-step
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32 screening strategy to identify true positives could improve the identification of
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34 psychologically distressed survivors who would most need and benefit from a
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36 psychological service. Second, by minimizing the number of false negatives in screening,
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38 we may minimize the number of misidentified and untreated distressed patients. Given the
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40 time constraints of most oncology clinics,^{15,25,69} it is particularly relevant to improve
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42 screening procedures that may help allocate better staff and services. When screening in
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44 practice, practitioners should consider complementing a first “ruling out” item by a second
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46 item focusing on case identification.
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51 Time necessary to fill the screen is an important criteria in selecting tools.^{15,25}
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53 Research has shown that ultra-short screening tools need to take fewer than 5 minutes, such
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3 as screening procedures of one to three items.^{46,65} The addition of one emotional item to
4 the DT, such as one from the PedsQL in our study, does respect this recommendation of
5 brevity.⁶⁹
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10 Notably, the terms used in the PedsQL emotional items evaluate precise targets like
11 sadness and concerns which are symptoms of depression and anxiety.⁴⁵ This is consistent
12 with a suggestion to add mood domains thermometers (anxiety, depression and anger
13 thermometers) to the DT to improve its efficacy, without increasing respondents' burden.⁴⁵
14 In terms of feasibility, the PedsQL questionnaire is widely used in research and practice in
15 oncology clinics to evaluate Quality of Life.^{61,70-72} This makes the individual emotional
16 items widely available for research and replication studies. Moreover, these items closely
17 resemble those of the Edmonton Symptom Assessment System (ESAS/ESAS-r).^{73,74} It is
18 thus probable that the improvement noted here in false negative and false positive rates
19 could extend to other instruments.^{12,42,43} Specifically, future two-step screening strategies
20 could make use of the problems list that is routinely used with the DT but was unfortunately
21 not available in our database.
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38 **Study limitations.** We must acknowledge the limitations of this study. First, the
39 sample was limited to childhood acute lymphoblastic leukemia survivors aged between 13-
40 40 years. Therefore, results should not be generalized to other populations of cancer
41 survivors or young children and elderly. Future research should include more diverse
42 samples representative of the population met in oncology clinics. Second, the reference
43 measures used to evaluate distress, depression and anxiety were self-report rating scales.
44 Although these tools are widely used to identify distress, depression, and anxiety, their
45 accuracy is lower than a structured diagnostic interview, an evaluation method not
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3 available in our database. So, case status on distress, depression and anxiety identified in
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5 the current study should be interpreted with caution. Finally, the developments made here
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7 should be replicated in validation studies on an independent sample to ascertain the
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9 predictive validity of strategies combining the DT with emotional items.
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11 12 **Conclusion**

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15 In conclusion, when combining the DT with individual emotional items to detect
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17 distress, depression, and anxiety in 255 pediatric cancer survivors, we showed improved
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19 performances over the DT alone, specifically in the accuracy of the detection of true
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21 positives. With the growing population of survivors, long-term follow-up clinics need to
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23 allocate their resources to most vulnerable subgroups. Screening technologies, such as the
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25 one exemplified here, will help identify vulnerable survivors more accurately. **Practitioners**
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27 **should consider complementing screening tools like the DT with focused items targeting**
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29 **patients' or families' issues.** Future research should confirm the interest of combining the
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31 DT with emotional questions to improve the accuracy of screening strategies.
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For Peer Review Only

TABLE 1 Sociodemographic and treatment characteristics of 255 survivors of childhood ALL from the PETALE/PSY-ALL cohort

Participants' characteristics	Adolescents (13-18 years) N=98 (38.4%) M (SD) or N (%)	Adults (19+ years) N=157 (61.6%) M (SD) or N (%)	Total sample N=255 M (SD) or N (%)
Sex			
Male	49 (50.0)	71 (45.2)	120 (47.1)
Female	49 (50.0)	86 (54.8)	135 (52.9)
Treatment site			
ANONYMIZED	84 (85.7)	134 (85.4)	218 (85.5)
ANONYMIZED	14 (14.3)	23 (14.6)	37 (14.5)
Age at diagnosis, years	3.8 (2.3)	7.8 (4.9)	6.3 (4.6)
Age at follow-up, years	15.8 (1.5)	25.6 (4.8)	21.8 (6.2)
Time since diagnosis, years	11.9 (2.6)	17.8 (5.0)	15.5 (5.1)
ALL risk status			
Standard risk	66 (67.3)	57 (36.3)	123 (48.2)
High risk	32 (32.7)	99 (63.1)	131 (51.4)
Unclassified	0 (0)	1 (0.6)	1 (0.4)
Radiotherapy			
Yes	37 (37.8)	108 (68.8)	145 (56.9)
No	61 (62.2)	49 (31.2)	110 (43.1)

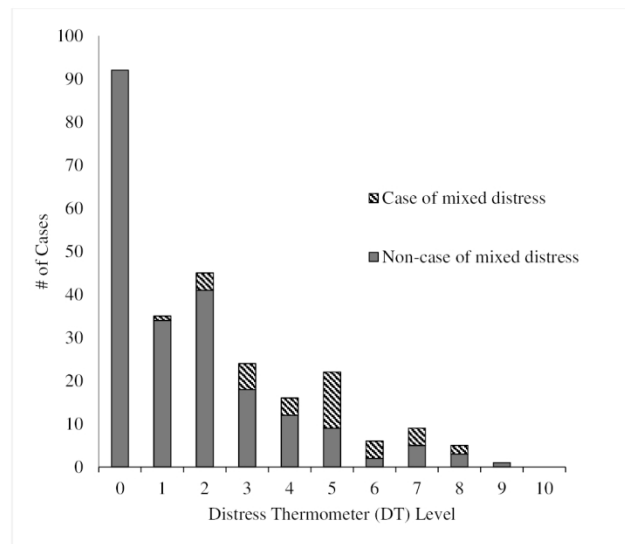


FIGURE 1 Frequencies of Distress Thermometer levels across psychological distress status in a sample of 255 childhood ALL survivors.

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TABLE 2 Comparison of clinical utility indices (CUI) for two-step strategies and the Distress Thermometer alone to detect distress, depression, and anxiety

Screening strategy	CUI- (95% CI)	CUI+ (95% CI)
Distress		
Strategy 1: DT \geq 2 + Concerns	0.81 (0.81-0.81)	0.37 (0.36-0.39)
Strategy 2: DT \geq 2 + Sadness	0.81 (0.81-0.81)	0.37 (0.36-0.39)
DT \geq 4	0.81 (0.80-0.81)	0.33 (0.31-0.34)
DT \geq 5	0.84 (0.84-0.85)	0.32 (0.31-0.39)
Depression		
Strategy 1: DT \geq 3 + Sadness	0.87 (0.87-0.88)	0.42 (0.40-0.43)
Strategy 2: DT \geq 2 + Sadness	0.82 (0.82-0.82)	0.35 (0.33-0.36)
DT \geq 4	0.82 (0.82-0.82)	0.32 (0.30-0.33)
DT \geq 5	0.87 (0.87-0.88)	0.36 (0.34-0.38)
Anxiety		
Strategy 1: DT \geq 2 + Concerns	0.80 (0.80-0.80)	0.29 (0.27-0.30)
Strategy 2: DT \geq 1 + Concerns	0.78 (0.78-0.79)	0.27 (0.25-0.29)
DT \geq 4	0.77 (0.77-0.88)	0.16 (0.14-0.18)
DT \geq 5	0.82 (0.82-0.83)	0.16 (0.14-0.18)

Note: CI, Confidence Interval; Concerns, Question on Concerns from the PedsQL; CUI-, Clinical Utility Index Negative; CUI+, Clinical Utility Index Positive; DT, Distress Thermometer; Sadness, Question on Sadness from the PedsQL; Reference measures for distress, depression, and anxiety, were derived from the Beck Youth Inventory, and the Brief Symptom Inventory-18.

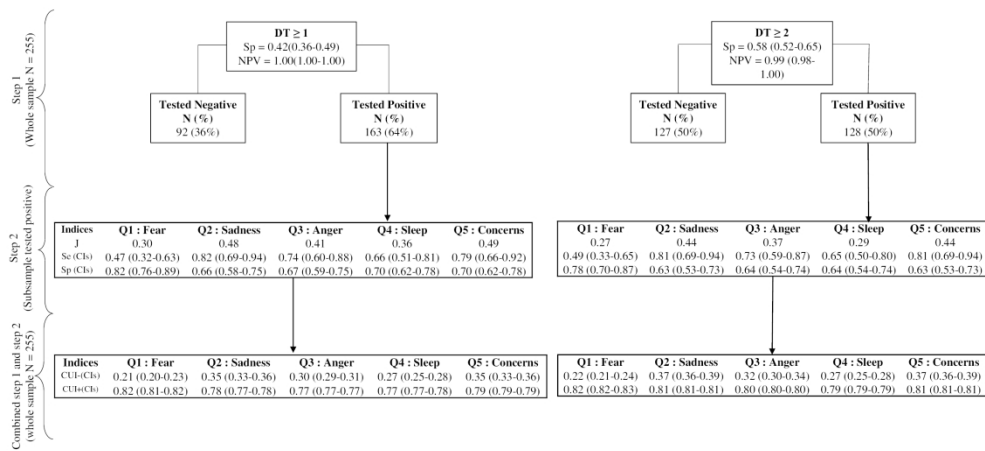
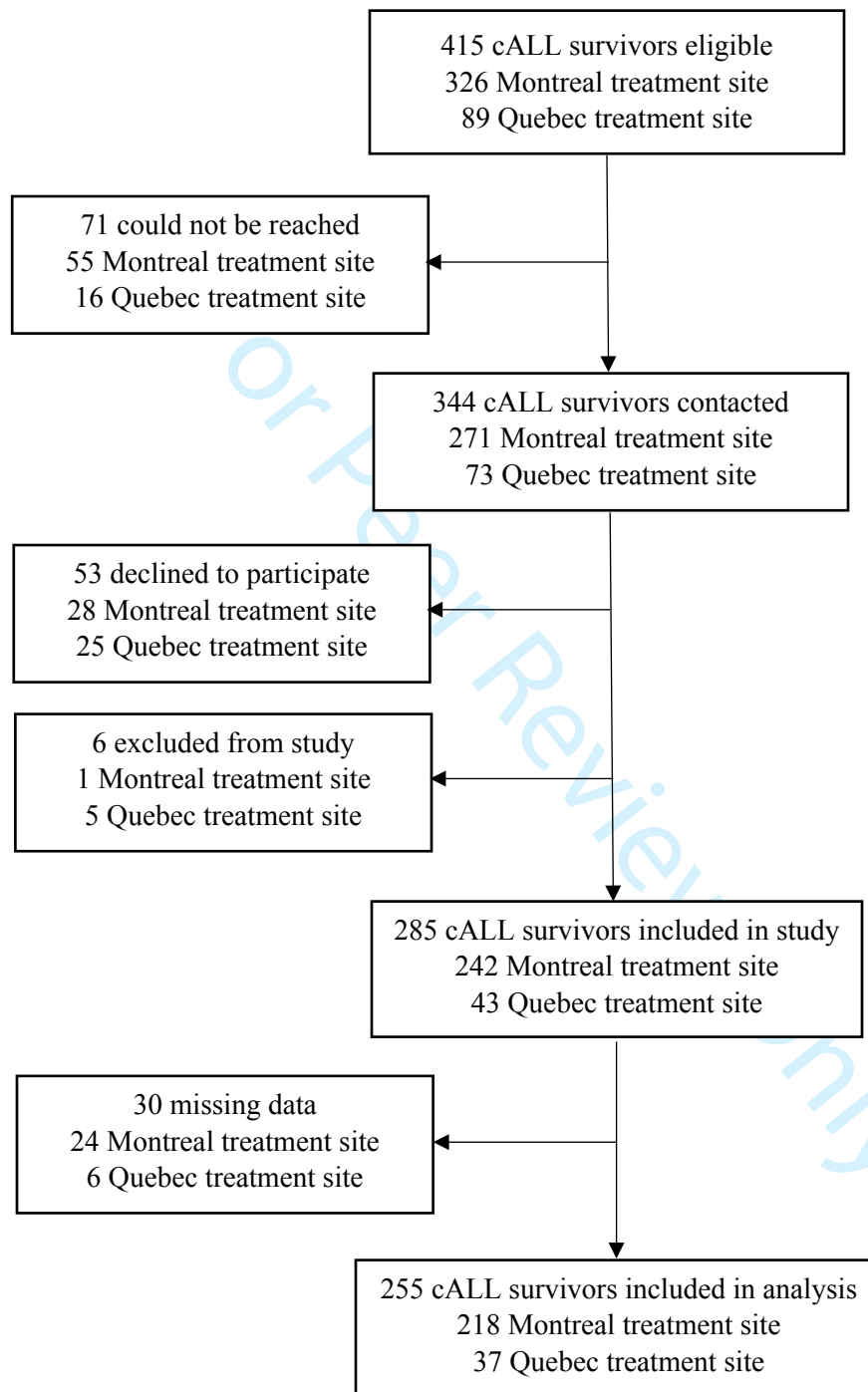


FIGURE 2 Summary of diagnostic indices and their 95% CI for two-step strategies screening for distress in a sample of 255 childhood ALL survivors.

Note. Step 1 consists in two alternative, DT ≥ 1 (left panel) and DT ≥ 2 (right panel). Step 2 consists of five alternatives by panel according to positivity of PedsQL emotional items. Step 2 is applied to individuals identified positives on Step 1. Aggregate indices for two-step strategies are available at the bottom. Abbreviations: Sp: Specificity; NPV: Negative Predictive Value; J: Youden J index; Se: Sensitivity; CI: Confidence Interval; CUI: Clinical Utility Index.

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Supplementary Figure S1. Flow chart



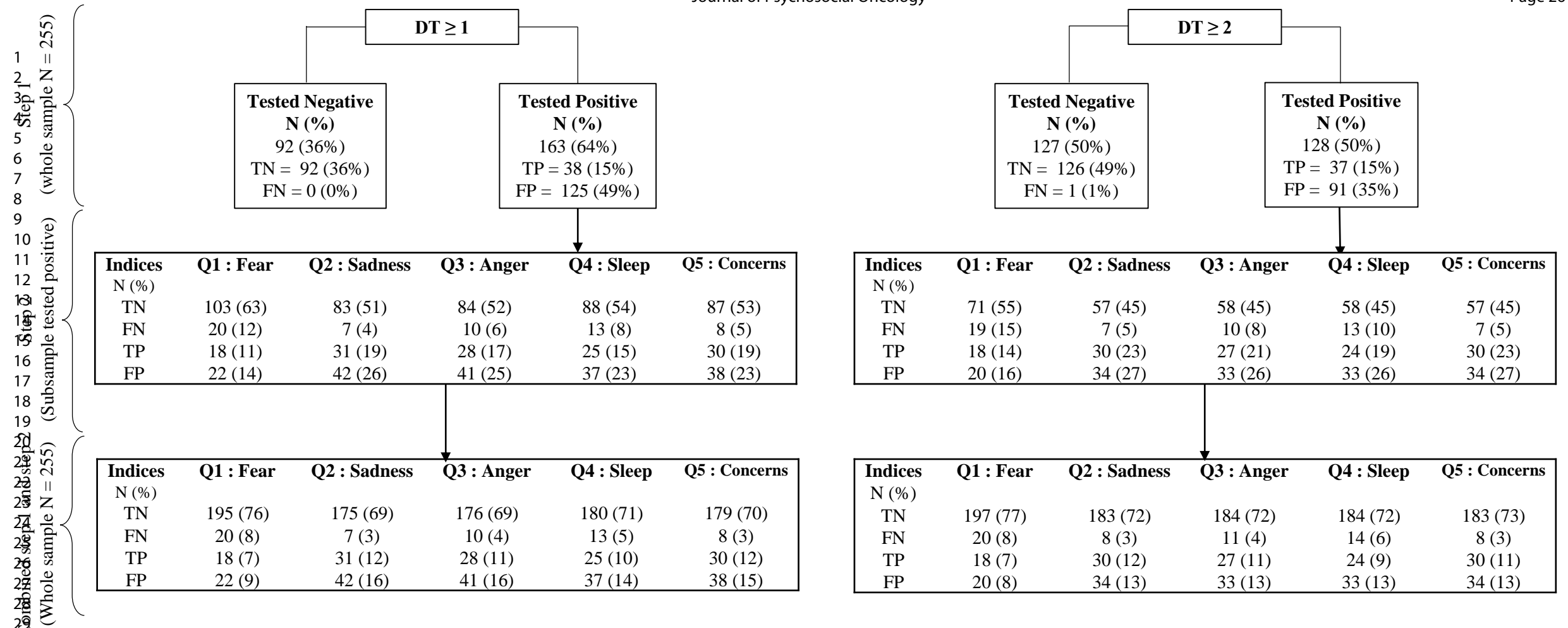


Figure S2.

Full description of true negatives TN, false negatives FN, true positives TP, and false positives FP, for two-step strategies screening for distress combining the Distress Thermometer with one emotional item from the PedsQL.

Note. Step 1 consists in two alternative, DT ≥ 1 (left panel) and DT ≥ 2 (right panel). Step 2 consists of five alternatives by panel according to positivity of PedsQL emotional items. Step 2 is applied to individuals identified positives on Step 1. Aggregate results for two-step strategies are available at the bottom.

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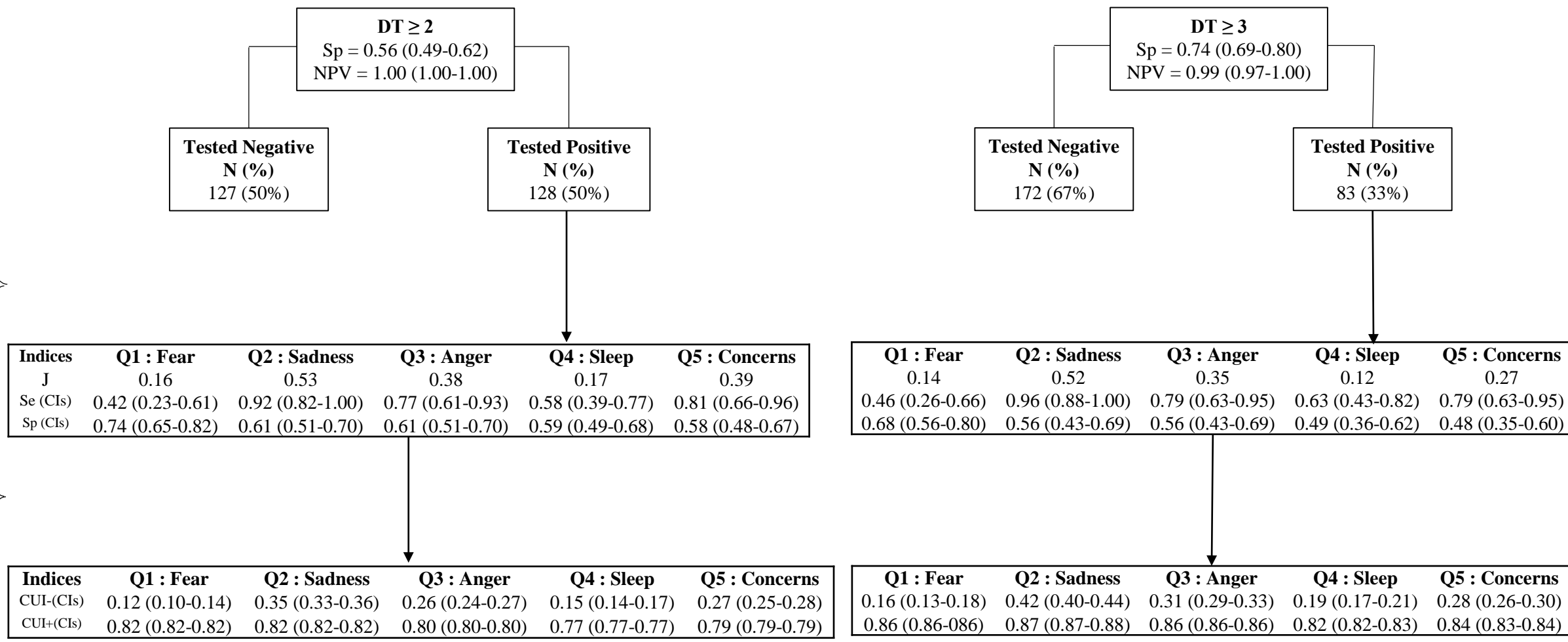


Figure S3.

Summary of diagnostic indices and their 95% CI for two-step strategies screening for depression in a sample of 255 childhood ALL survivors.

Note. Step 1 consists in two alternative, DT≥1 (left panel) and DT≥1 (right panel). Step 2 consists of five alternatives by panel according to positivity of PedsQL emotional items. Step 2 is applied to individuals identified positives on Step 1. Aggregate indices for two-step strategies are available at the bottom. Abbreviations: Sp: Specificity; NPV: Negative Predictive Value; J: Youden J index; Se: Sensitivity; CI: Confidence Interval; CUI: Clinical Utility Index.

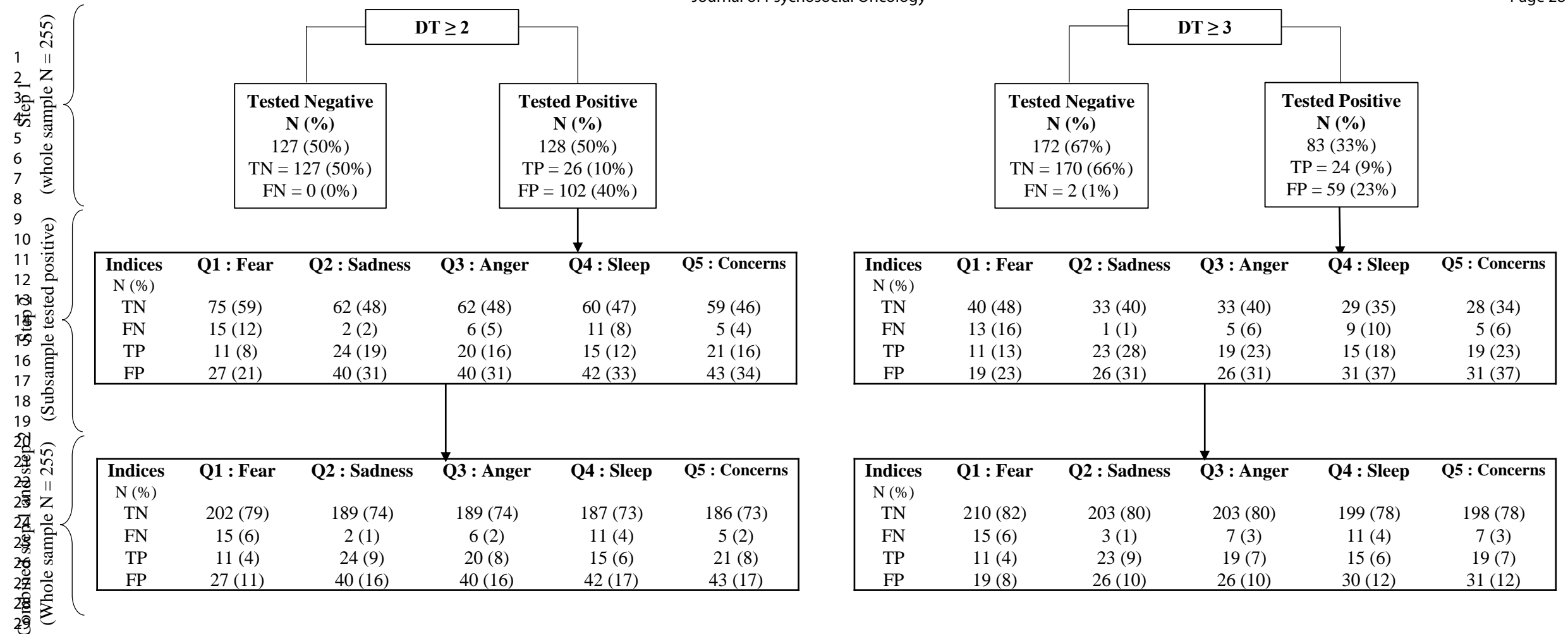


Figure S4.

Full description of true negatives TN, false negatives FN, true positives TP, and false positives FP, for two-step strategies screening for depression combining the Distress Thermometer with one emotional item from the PedsQL.

Note. Step 1 consists in two alternative, DT ≥ 1 (left panel) and DT ≥ 1 (right panel). Step 2 consists of five alternatives by panel according to positivity of PedsQL emotional items. Step 2 is applied to individuals identified positives on Step 1. Aggregate results for two-step strategies are available at the bottom.

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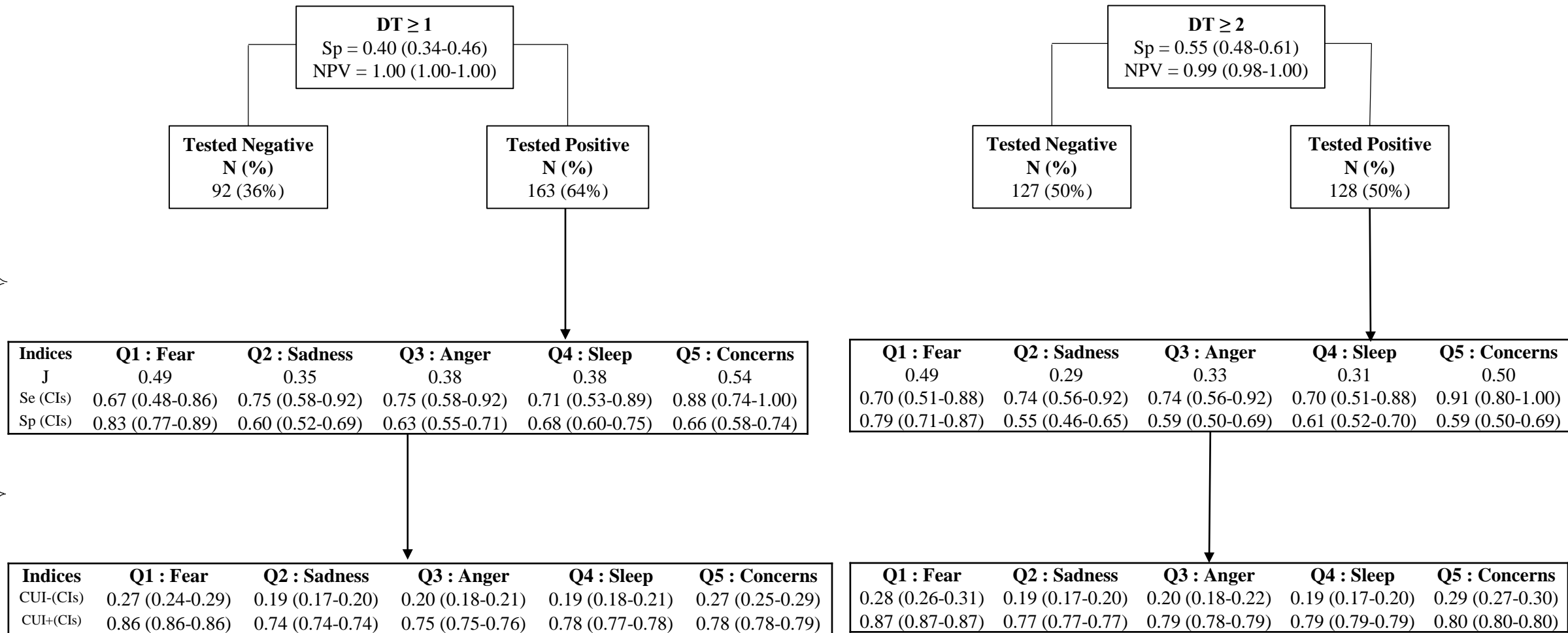


Figure S5.

Summary of diagnostic indices and their 95% CI for two-step strategies screening for anxiety in a sample of 255 childhood ALL survivors.

Note. Step 1 consists in two alternative, DT≥1 (left panel) and DT≥1 (right panel). Step 2 consists of five alternatives by panel according to positivity of PedsQL emotional items. Step 2 is applied to individuals identified positives on Step 1. Aggregate indices for two-step strategies are available at the bottom. Abbreviations: Sp: Specificity; NPV: Negative Predictive Value; J: Youden J index; Se: Sensitivity; CI: Confidence Interval; CUI: Clinical Utility Index.

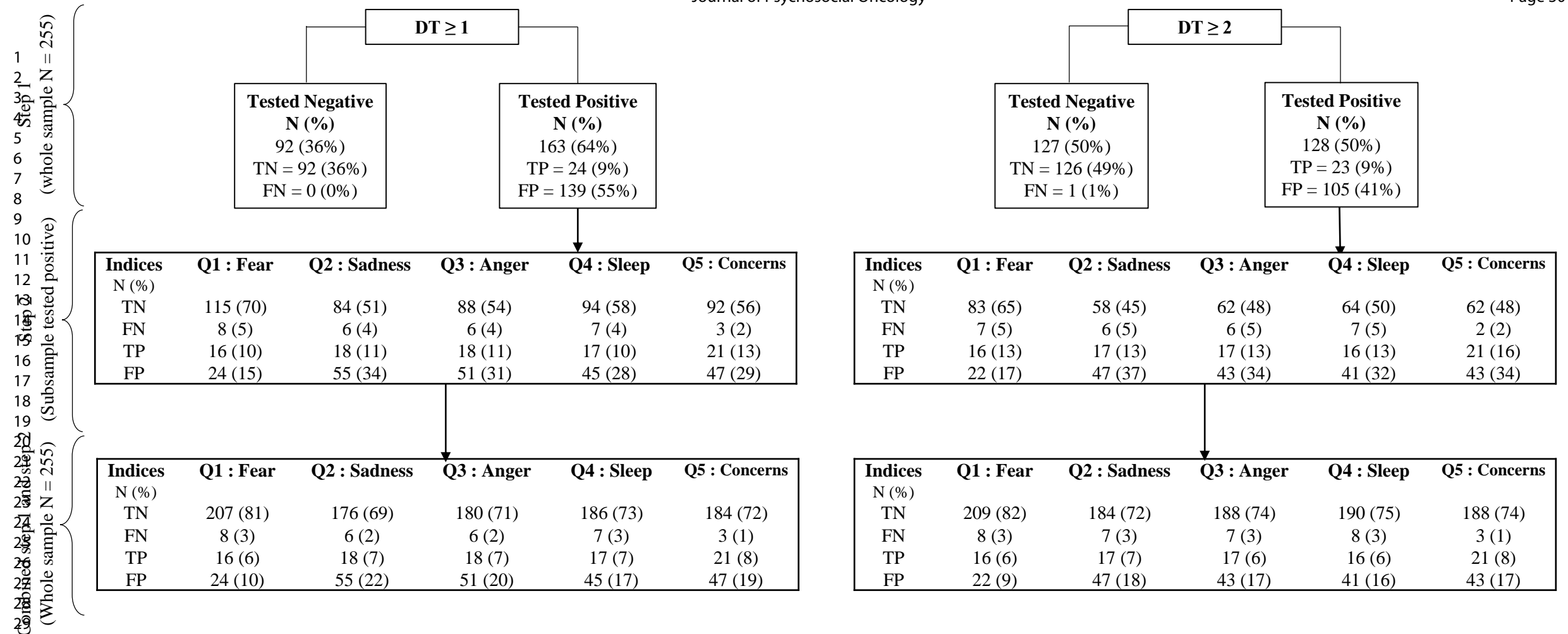


Figure S6.

Full description of true negatives TN, false negatives FN, true positives TP, and false positives FP, for two-step strategies screening for anxiety combining the Distress Thermometer with one emotional item from the PedsQL.

Note. Step 1 consists in two alternative, DT ≥ 1 (left panel) and DT ≥ 2 (right panel). Step 2 consists of five alternatives by panel according to positivity of PedsQL emotional items. Step 2 is applied to individuals identified positives on Step 1. Aggregate results for two-step strategies are available at the bottom.