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Validation of the Asthma Severity Scoring System (ASSESS) in the ALLIANCE cohort

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CONFLICT OF INTEREST:

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ABSTRACT (250/250 words)

Background:

The Asthma Severity Scoring System (ASSESS) quantifies asthma severity in adolescents and adults. Scale performance in children < 12 years is unknown.

Objective: To validate the ASSESS score in the All Age Asthma Cohort (ALLIANCE) and explore its use in children <12 years.

Methods: Scale properties, responsiveness, and known-group validity were assessed in 247 children (median age 11 years, IQR: 8-13 years) and 206 adults (median age 52 years, IQR: 43-63 years).

Results: Overall, measures of internal test consistency and test-retest reliability were similar to the original data of the Severe Asthma Research Program (SARP). Cronbach's α was 0.59 in children 12–18 years and 0.73 in adults, reflecting the inclusion of multiple and not always congruent dimensions to the ASSESS score especially in children. Analysis of known-group validity confirmed the discriminatory power, as the ASSESS score was significantly worse in patients with poor asthma control, exacerbations and increased salbutamol use. In children between 6–11 years test reliability was inferior compared to adults and adolescents (Cronbach's α 0.27) mostly due to a less lung function impairment in asthmatic children of this age group. Known-group validity however confirmed good discriminative power regarding severity-associated variables similar to adolescents and adults.

Conclusion:

Test reliability and validity of the ASSESS score was confirmed in the ALLIANCE cohort. In children aged 6-11 years internal consistency was inferior compared to older asthma patients, however test validity was good and encourages age-spanning usage of the ASSESS score in all asthma patients ≥ 6 years.

CLINICAL IMPLICATIONS

The ASSESS score is a valid and useful instrument to quantify asthma severity in adults and children 12–18 years. First evidence additionally supports usage in children 6–11 years.

CAPSULE SUMMARY

The multidimensional ASSESS score is a valid and reliable measure for asthma severity in patients from 12 years onwards and can also be applied in children 6-11 years as validated in the ALLIANCE cohort.

KEY WORDS:

ALLIANCE
Asthma
Asthma control
Asthma severity
Children
Pediatric asthma
Adult asthma
Validation study

ABBREVIATIONS

ACT	Asthma Control Test

183	ALLIANCE	ALL Age Asthma Cohort
184	ASSESS	Asthma Severity Scoring System
185	CASI	Composite Asthma Severity Index
186	FEV_1	Forced Expiratory Volume in 1 second
187	ICC	Intra-class correlation coefficient
188	MID	Minimal important difference
189	SD	Standard deviation
190	SEM	Standard error of measurement

INTRODUCTION

Asthma is one of the most prevalent chronic respiratory diseases worldwide and affects patients of all ages.[1-3] It is a heterogeneous disease driven by chronic inflammation and structural remodeling of the airways resulting in variable expiratory airflow limitations and symptoms such as wheeze, cough and shortness of breath.[4, 5] According to the Global Initiative of Asthma (GINA) guidelines, assessment of asthma patients in primary care usually encompasses evaluation of asthma control as well as severity.[4, 6]

Measuring asthma severity is complex and several clinical dimensions can be used as a proxy, for example asthma symptoms including exacerbations, lung function impairment and level of controller medication. The GINA guideline proposes to assess asthma severity retrospectively by the level of controller medication a patient needs to achieve and maintain asthma control.[4, 7] However, this classification has some shortcomings; it works well for patients with severe asthma, as it identifies those patients with increased risk for adverse outcomes and who could benefit from further investigations and treatment with biologicals. In contrast, patients with "mild" asthma according to their low levels of asthma medications might still be at risk for exacerbations and even fatal outcomes, especially in patients with infrequent symptoms.[8] Another guideline recommends using symptom intensity and lung function in patients without prior controller medication[9], however many patients seen in tertiary centers or included in cohort studies are already treated with controllers.

Lastly, the Composite Asthma Severity Index (CASI) comprises medication, lung function as well as symptom burden, but has only been evaluated in children[10]. In contrast, the recently published Asthma Severity Scoring System (ASSESS) score is a multidimensional instrument and has been developed for children ≥ 12 years and adults.[11] The ASSESS score captures symptom load via weighted scores of the Asthma Control Test (ACT)[12], as well as lung function, current medications, and exacerbations in the past 6 months. Promising

characteristics regarding measurement properties, responsiveness to therapeutic intervention, and its association with various asthma outcomes have been confirmed.[11] Nonetheless, in their conclusion, the authors called for additional validation studies before using the ASSESS score in a broader context.[11] Furthermore, asthma affects children of all age groups, therefore instruments of asthma control and severity should ideally encompass all age groups. Until now, it is unknown if the ASSESS score can also be applied to children < 12 years.

Using data from the All Age asthma cohort (ALLIANCE) recruiting children with preschool wheeze as well as children, adolescents and adults with asthma, we aimed to validate the measurement properties of the ASSESS score in an independent cohort. Furthermore, we analyzed the performance of the ASSESS score in children 6–11 years with predominately mild-to-moderate asthma.

METHODS

Study design

We analyzed data from the prospective, observational, multi-center All Age Asthma Cohort (ALLIANCE) study, which recruits pediatric and adult asthma patients from age 6 years onwards with asthma diagnosed according to GINA[4] and German national guidelines[13] at seven hospitals across Germany. Children < 6 years with recurrent preschool wheeze are recruited in an additional study arm but were not part of the present study. The study was approved by local Ethic Committees and parents of underage study participants gave informed consent as well as study participants from eight years of age onwards. The study was registered at *clinicaltrials.gov* (pediatric arm: NCT02496468 and adult arm: NCT02419274).

Further details regarding study design, inclusion and exclusion criteria have been published elsewhere.[14] In this study, all asthma patients ≥ 6 years with available data to calculate the ASSESS score from the pediatric and adult study arm were included (see Figure E1 in the Online Repository). Spirometry values were analyzed as percent predicted values using published reference equations.[15] Further details regarding clinical variables used are specified in the Online Repository.

ASSESS score calculation

The ASSESS score was calculated in each patient as described previously, ranging from 0 to 20 points, with 20 points denoting the most severe score.[11] The score consists of four components, namely symptom load (ACT scores), lung function (FEV_1% predicted), medication, and exacerbations (i.e., systemic corticosteroid requirement and/or hospitalization in the previous 12 months due to asthma symptoms). The various categories within each component and their equivalent ASSESS score points are displayed in **Table 1**.

Some adaptions to the ASSESS scoring system were necessary due to the information available in the ALLIANCE dataset: The original publication from the SARP cohort refers to the past six months regarding exacerbations in most but not all time points assessed for score validity.[11] Our analyses always included data from the past 12 months for exacerbation data. Similarly, the original publication referred to medication taken at the study visit when calculating "recent medication use" while our analyses refer to any regular medication taken in the past 4 weeks. Lastly, for children 6–11 years we used the Childhood Asthma Control Test.[16] Further information can also be found in the Online Repository.

Data analysis and statistics

Cronbach's α was calculated to evaluate internal consistency between score components. Test-retest reliability between ASSESS scores at baseline and at 12 months follow-up was assessed by computing the intra-class correlation coefficient (ICC) based on a two-way random effects model. The minimal important difference (MID) was calculated in a distribution-based fashion using two established MID definitions, as previously described also for ASSESS.[17, 18] MID=0.5*standard deviation (SD) and MID=1*standard error of measurement (SEM). Correlations were evaluated using Spearman's method.

Differences between groups were tested using the Mann-Whitney *U* test for two groups and the Kruskal-Wallis test followed by Dunn's test for multiple comparisons for three groups. For descriptive statistics, we used mean and standard deviation (SD), median and interquartile range (IQR) as appropriate and p-values were calculated using Wilcoxon-Test or Chi-square test.

To test the construct validity of ASSESS in the absence of a reference standard, the score was compared between a set of categories that were hypothesized to reflect different levels of asthma severity (known-group validity).[19] These categories were uncontrolled asthma according to GINA, occurrence of ≥1/ ≥2 steroid-requiring exacerbation(s), ≥1 hospitalization in the past 12 months, emergency doctor visits due to wheeze and hospital stays with oxygen requirement in the past 12 months (children only).

In pediatric patients, to reflect the higher prevalence of mild-to-moderate asthma in this patient group, ASSESS scores were additionally compared between patients classified by ≥2 salbutamol-requiring wheezing episodes during the past year and by months of salbutamol-use in the past year (none vs. <1–7 months vs. ≥8 months). To examine score changes over time, changes in ASSESS scores between baseline and follow-up were compared in patients with a clinically relevant improvement of asthma control (ACT increase of ≥3 points) and lung

function (≥10% increase of FEV_1 % predicted value). All statistical analyses were performed with R (version 4.1).[20]

RESULTS

Patient characteristics

In total, 247 of 298 (83%) asthmatic children had all available data to calculate the ASSESS scores at baseline and were included in the study, with 140 children aged 6–11 years and 107 children aged 12–18 years. In the adult cohort, the ASSESS score was available in 206 of 218 (94%) patients. (**see Figure E1 in the Online Repository**). The median age in the pediatric cohort was 9 years (IQR: 8–11 years) in children aged 6–11 years and 14 years (IQR: 13-15 years) in children aged 12–18 years, while it was 52 years (IQR: 43–63) in the adult cohort. The age groups differed considerably regarding severity-associated clinical characteristics; adult asthma patients showed more uncontrolled asthma, lower FEV_1 and a higher percentage of patients with high-dose ICS or regular systemic steroid treatment. Further details on baseline patient characteristics in pediatric and adult patients are summarized in **Table 2.**

ASSESS score distribution

The distribution of baseline ASSESS scores across different age groups is depicted in **Figure 1**. The mean ASSESS score was significantly lower at baseline in both pediatric cohorts with 3.9 points (SD: 2.6; range: 0–12) in children aged 6–11 years and 3.9 (SD: 3.2; range: 0–18) in children aged 12–18 years compared to adults with 8.5 points (SD: 4.4; range: 0–20), indicating an overall higher severity of asthma in the adult cohort ($p < 0.001$, **Table 3**).

There was no significant difference of mean baseline ASSESS scores between children of 6–11 years and 12–18 years (3.9 points (SD 2.6; range; 0–12) vs. 3.9 points (SD 3.2; range: 0–18, **Table 3**). Neither was there a significant score difference between male and females in

neither the pediatric nor adult cohort (data not shown). The ASSESS score remained stable between baseline and 12 months follow-up in children. The 12 months ASSESS score was 3.3 points (SD: 2.4; range: 0–14) and 3.3 points (SD: 2.9; range: 0–16) in children aged 6–11 years and those aged 12–18 years, respectively. In adults, a substantially lower ASSESS score was seen at 12-months (5.7 points; SD: 3.1; range: 2–16).

Scale properties

Internal consistency of the ASSESS score components at baseline, measured by Cronbach's α, was 0.27 (0.07–0.47) in children aged 6–11 years and 0.59 (0.47–0.70 in children 12–18 years, while it was 0.73 (0.67–0.79) in the adult cohort (**see Table E1 A-B in the Online Repository**). Thus, internal consistency was comparable to the original publication[11] in regard to adults and children between 12–18 years but lower in younger children mostly due to the poor correlation of lung function with the other scale items.

The test-retest reliability in participants with available baseline and 12-months follow-up scores using ICC estimates based on two-way random-effects models was 0.47 (0.29–0.62) in children 6-11 years, 0.78 (0.63–0.86) in children 12–18 years, and 0.64 (0.42–0.77) in adults. The ICC estimate in adults was slightly lower than in the original publication[11] and indicates moderate – good test-retest reliability.[17] Again, children of 12–18 years showed overall higher ICC than children of 6–11 years.

The original publication identified a minimal important difference (MID) of 2 points. Concordantly, we found a similar MID in adults with 2.20 calculated according to the 0.5*SD method and 2.30 (1*SEM method) in adult asthma patients. The MID in children trended lower and depended more on the method applied than the adult MIDs (1.3 [0.5*SD method] and 2.1 [1*SEM method] and 1.6 [0.5*SD method] and 2.1 [1*SEM method] in children 6-11 years and 12-18 years, respectively).

In the adult cohort, ASSESS scores were found to be moderately negatively correlated with FEV_1 % predicted values (Spearman's rho: -0.61, p<0.001) and FEV_1/FVC predicted values (Spearman's rho: -0.47, p<0.001). In children 6-11 years, neither the FEV_1% predicted values nor the FEV_1/FVC predicted values correlated with ASSESS scores (FEV_1% predicted values: Spearman's rho: -0.02, p=0.803; FEV_1/FVC predicted values: Spearman's rho: -0.01, p=0.933). Children 12-18 years showed a weak correlation between the ASSESS scores and FEV_1/FVC predicted values in children (Spearman's rho: -0.26, p=0.007), but not between ASSESS scores and FEV_1% predicted values (Spearman's rho: -0.11, p=0.254).

Increased asthma severity is associated with reduced asthma related quality of life (QoL). This was also reflected in the ASSESS score, which was inversely correlated with the asthma quality of life questionnaire (AQLQ) scores in adults (Spearman's rho: -0.68, p<0.001) at baseline (**see Figure E2 A in the Online Repository**). Data regarding QoL was not available for children.

Known-group validity

To test the construct validity of ASSESS in adults, the score was compared between patients that were hypothesized to have different levels of asthma severity. Patients with ≥1 steroid-requiring exacerbation(s) or ≥1 hospitalization in the previous year had significantly higher mean ASSESS scores compared to patients who did not experience those events. This was observed in adult patients as well as in both pediatric age subgroups (**Figure 2 A, B and Table 4 A-C**). A statistically significant difference in ASSESS scores could also be seen between GINA control ratings, with significantly increasing mean ASSESS scores from controlled to partly and uncontrolled asthma in both pediatric cohorts and in adults (**Figure 2 C**). In adults, a clinically relevant increase of 0.5 in the AQLQ between baseline and 12 months follow-up, indicating improvement of quality of life, was associated with in a significant reduction of the ASSESS score, i.e. asthma severity (**Table 4C, Figure E2 B in the Online Repository**).

Patients with an ACT increase of ≥3 points[21] at 12 months follow-up showed on average a significantly greater ASSESS score decrease compared to those without such an increase, which we observed in both pediatric cohorts and adults (**Figure 2 D and Table 4 A-C**). Furthermore, adults with an increase of ≥10% in FEV_1% predicted values between baseline and 12 months follow-up also had a significantly improvement (decrease) of the ASSESS score (**Figure 2 E and Table 4B**). In the pediatric cohort, this difference was not statistically in either children aged 6-11 years not those aged 12–18 years (**Figure 2 E in the Online Repository; Table 4 A-B**).

In children, we additionally analyzed responsiveness of the ASSESS score with regard to clinical variables not involved into the ASSESS score components. Children in both age groups with emergency doctor visits had significantly higher ASSESS scores than those without (**Figure 3A in the Online Repository; Table 4 A–B**).. Likewise, children in both age groups who required oxygen during a hospital stay at least once in the past 12 months scored significantly higher on the ASSESS score than those who did not (**Figure 3B in the Online Repository; Table 4 A–B**).

We observed responsiveness of the ASSESS score related to wheezing episodes per year (≥2 wheeze episodes with more than 2 days of salbutamol use) and the amount of reliever needed in the previous 12 months (months with salbutamol use). Children who experienced ≥2 wheezing episodes in the past year had significantly higher ASSESS scores, indicating more severe asthma. (**Figure 3 C in the Online Repository; Table 4 A–B**). Equally, children who used salbutamol in 8 or more months displayed the highest mean ASSESS score in both pediatric age groups compared to children without any salbutamol use in the past 12 months. In children of 12–18 years, a significant difference in ASSESS scores was also seen in children with at least 8 months of salbutamol use compared to children with 1-7 months of salbutamol use (**Figure 3D**).

DISCUSSION

The ASSESS score is a newly proposed instrument to quantify asthma severity in adolescents and adults. Here, we evaluated the performance of the ASSESS score in the ALLIANCE cohort, a multi-center, combined pediatric and adult asthma cohort, addressing the need for further external validation.

Overall, our analysis showed comparable reliability and validity in adults and children older than 12 years as the original publication[11], confirming the utility of the ASSESS score with data from an independent asthma cohort. Furthermore, we demonstrate for the first time that the ASSESS score can also be applied to children aged 6-11 years, thus emphasizing the usefulness of this instrument to measure asthma severity across all age groups ≥ 6 years unlike previously published asthma severity scores[10].

Still, scale reliability metrics like internal consistency and test-retest reliability were lower in children of 6-11 years. In general, internal consistency was not expected to be excellent in all age groups [10, 11], as the ASSESS score aimed to incorporate distinct dimensions of asthma severity (medication, lung function, symptoms and exacerbations), which do not necessarily behave concordantly in all patients. For example, some patients might have poor lung function but still perceive their asthma as controlled. This can lead to a lower consistency among score components which was particularly evident in the pediatric age group, especially in children between 6-11 years who had a markedly lower Cronbach's α compared to adolescents and adults. Specifically, the dimension lung function was not as important to the overall ASSESS score as in adults (**Table E1 in the Online Repository**) which was also reflected by the poor correlation between the ASSESS score and FEV_1 % predicted in children compared to adults. This was consistent with previous data showing that FEV_1 correlates poorly with symptom-based severity in children.[22-25] In general, many children with an asthma diagnosis according

413 to guidelines show a normal lung function test with a FEV_1 > 80% predicted [25-29] and lung
414 function therefore cannot contribute to the ASSESS sum score in these children (see Table 1).
415 In contrast, the Composite Asthma Severity Index (CASI), an asthma severity score for
416 children used a higher FEV_1 cut-off of 85%, however this did also not improve internal score
417 consistency[10].
418 Although lung function seemed to be less important for severity assessment in the younger age
419 groups and therefore impacted negatively on the scores' internal consistency, it is an important
420 dimension of asthma severity in adolescents and adults. This further emphasizes the need for a
421 composite score capturing multiple dimensions of asthma severity, particularly if the aim is to
422 apply it across all age groups and outweighs the negative impact of lung function for the
423 internal consistency in the youngest age group. ASSESS scores differed significantly between
424 groups that were hypothesized to have different asthma severity levels, demonstrating good
425 known-group validity. Some of the groups were dichotomized by variables that are part of the
426 ASSESS score, which makes the detected differences probable. Still, this indicates that the
427 ASSESS is a good alternative option in clinical studies to reflect the overall asthma severity
428 compared to reporting single variables. Additionally, we were able to show good known-group
429 validity for clinical variables not included into the ASSESS score such as the number of wheeze
430 episodes and salbutamol use over the past 12 months in children and AQLQ in adults.
431 Furthermore, we also found good known-group validity in children aged 6–11 years for most
432 variables tested, further supporting the utility of the ASSESS score as a useful and valid
433 measure for asthma severity even in young children.
434 In our study, pediatric patients suffered mostly from mild-to-moderate asthma, as opposed to
435 the more severe disease spectrum in the adult cohort. This was also reflected by generally lower
436 ASSESS scores. The ASSESS score showed the ability to distinguish not only groups in regard
437 to severe events (steroid-requiring exacerbations, hospitalizations), but also between milder

438 outcomes (≥2 salbutamol-requiring wheezing episodes, months of salbutamol use). However,
439 mean score differences between groups were generally smaller in the pediatric cohort
440 compared to the adult cohort, especially regarding the milder outcomes.
441 Although quantifying asthma severity has long been identified as a need for asthma patient care
442 and research, only few instruments exist. The CASI is overall similar to the ASSESS score in
443 regards to the clinical dimensions included, however has only been validated for children and
444 adolescents[10]. Additionally, information on asthma symptoms is restricted to days and nights
445 with SABA use, while the ASSESS score relies on the ACT which includes more diverse
446 information about the patients' perception of asthma symptoms. Additionally, the ACT is
447 widely used in clinical and research settings which makes it possible to analyze the ASSESS
448 score retrospectively. Several categorical classifications have been developed as well[22, 30, 31]
449 including using the GINA treatment steps as proxy for severity[4]. However, categorical
450 classification systems often lack discriminative power, particularly if more than one dimension
451 of asthma severity is included. Peer et al. for example developed an instrument based on the
452 severity assessment proposed by the National Heart, Lung and Blood Institute[9] in which the
453 worst severity observed in four clinical categories (symptoms, FEV1, medication and ICD-10
454 code for asthma severity) defined the overall severity. This approach cannot differentiate if a
455 patient shows high severity in only one or all four dimensions.[31] Instruments based on scores
456 as the ASSESS score are not only able to incorporate and weigh different dimensions but also
457 offer a continuous scale advantageously for scientific analysis.
458
459 Strengths of this study include the multi-center, prospective study design and inclusion of
460 children as well as adults in the same study which allowed us to study and compare the ASSESS
461 score across different age groups. Furthermore, we were also able to evaluate known-group

validity in children encompassing independent variables that were not part of the ASSESS score.

We note several limitations to our study. A conceptual limitation lies in the fact that there is no reference standard for asthma severity to which the ASSESS score could be compared. Furthermore, as the ALLIANCE cohort is a purely observational cohort, we were not able to validate changes of the ASSESS score after a defined treatment intervention. Instead, ASSESS scores were compared between groups that were hypothesized to have different levels of asthma severity also resorting to criteria that were part of the ASSESS score. However, variables not included into the ASSESS score and not explored in the original publication additionally supported the known-group validity. Yet, while our results indicate that the ASSESS can be used as a tool to compare asthma severity between groups, a single ASSESS score in an individual patient without a longitudinal reference measurement might be of only limited value. Additionally, we note that there is a lack of severe asthma cases in the pediatric asthma cohort aged 6–11 years and there is a need to validate the ASSESS score in this patient group.

Therefore, further follow-up data from the ALLIANCE cohort and additional studies are warranted that examine the ASSESS score over a longer course of time and to explore characteristics of the ASSESS in relation to biomarkers associated with severity and its responsiveness to therapy. Additionally, a possible role of the ASSESS score in clinical practice and individual patient care needs further attention. Lastly, due to the important changes of the GINA 2019 recommendations[32] regarding treatment of mild asthma, the ASSESS score should be amended in the future to include “as needed” ICS-formoterol use with appropriate evaluation of these changes.

In conclusion, this study could externally replicate results regarding important measurement characteristics of the ASSESS in an independent cohort of pediatric and adult asthma patients

covering an extended age-range and the whole spectrum of mild to severe disease. Our results support the application of the ASSESS score, particularly in asthma cohorts covering the transition from childhood to adulthood or mixed age cohorts, thus rendering it an important tool for epidemiological research. Future studies are needed to confirm its use in children between 6 - 11 years of age and evaluate its application in a clinical context or interventional trials.

ETHICS

The ALLIANCE study was approved by the local ethics committees (leading ethics committee: University of Luebeck, Ethics Committee; reference no. AZ 12-215). All adult participants provided written informed consent prior to enrolment in the study. In children, informed consent was obtained from either parents or legal representatives if aged younger than 8 years, and additionally by the child if aged 8 years or older.

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FIGURE LEGENDS

Figure 1: Asthma severity according to ASSESS scores across different age groups (6–75 years).

Figure 2. ASSESS Score in relation to measures of asthma control and severity

ASSESS scores in patients with ≥1 exacerbation (2 A), ≥1 hospitalization (2 B) in the previous year, and stratified by GINA control status (2 C). Change of ASSESS score between baseline and 12-months follow-up was compared in patients with clinical relevant improvement of asthma control (ACT increase by ≥3 points) (2D) and lung function (FEV_1 increase ≥10%) (2E) during the same period. Mann-Whitney *U* test was used for two groups and the Kruskal-Wallis test followed by Dunn's test for multiple comparisons for three groups (* $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$).

Figure 3: ASSESS scores and wheezing episodes and salbutamol use in the past 12 months in children.

Assess scores in children with asthma with ≥ 2 wheeze episodes in the past 12 months (3A) and in children with no salbutamol use, 1-7 months with at least once salbutamol use and ≥ 8 months with at least once salbutamol use (3B), with ≥ 1 emergency doctor visit due to wheeze in the past 12 months (3C), with at least one hospitalization requiring oxygen treatment (4D)

Mann-Whitney *U* test was used for two groups and the Kruskal-Wallis test followed by Dunn's test for multiple comparisons for three groups (* $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$)

Table 1: Calculation of the ASSESS score.

Component	ACT score	ASSESS score
	23-25 points (in children 6-11 years: 24-27 points[1])	0 points
	20-22 points (in children 6-11 years: 20-23 points[1])	1 point
	17-19 points	2 points
	14-16 points	3 points
	11-13 points	4 points
	8-10 points	5 points
	5-7 points	6 points
Lung function	**FEV_1% predicted**	**ASSESS score**
	≥ 80% predicted	0 points
	70-80% predicted	1 point
	60-70% predicted	2 points
	<60% predicted	3 points
Asthma treatment[2]	**Current medication**	**ASSESS score**
	No treatment	0 points
	Albuterol only	1 point
	Low-dose[3] ICS only or LTRA only	2 points
	Low-dose ICS & at least 1 controller4 or medium-dose[3] ICS only or high-dose[3] ICS only	3 points
	Medium-dose ICS & at least 1 controller or high-dose ICS & at least 1 controller	4 points
	High-dose ICS & at least 2 controllers	5 points
	Systemic corticosteroids	1 point
	Current biologic	1 point
Exacerbations[5]	**Exacerbation**	**ASSESS score**
	Prednisone burst	2 points
	Prednisone burst + hospitalization[6]	4 points

The table shows the five components (left column) of the ASSESS score and their weighting. The final score is calculated by summing up the points from each component to a maximum score of 20 with higher scores indicating increased asthma severity. [1]In children aged 6-11 years, the Childhood ACT was used. [2]In ALLIANCE, "recent" medication (i.e., use in the past 4 weeks) was documented for each study visit. [3]Low, middle and high-dose ICS were defined according to GINA guideline using age-dependent and substance-specific cut-offs. [4]Controllers are LTRA, LABA, LAMA, Theophylline (for step 5 also low-dose oral corticosteroids). Pediatric patients only received LABA and LRTA. [5]Prednisone bursts and hospitalizations refer to the past 12 months.

ACT: Asthma Control Test; ASSESS: Asthma Severity Scoring System; FEV1: Forced Expiratory Volume in 1 second; ICS: Inhaled Corticosteroids; LABA: Long-acting beta agonist; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonist.

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694 **Table 2:** Patient characteristics.

Variable	Children 6–11 years (n=140)	Children 12–18 years (n=107)	Adult cohort (n=206)	P-Value
Age (years)	9 (IQR: 8–11)	14 (IQR: 13–15)	52 (IQR: 43–63)	*a:* <0.001 *b:* <0.001 *c:* <0.001
Sex				*a:* 0.019
Female	39 (28%)	47 (44%)	117 (57%)	*b:* <0.001
Male	101 (72%)	60 (56%)	89 (43%)	*c:* <0.001
GINA control				
Uncontrolled	12 (9%)	16 (15%)	79 (38%)	*a:* N.S.
Partly controlled	44 (31%)	40 (37%)	76 (37%)	*b:* <0.001
Controlled	84 (60%)	51 (48%)	51 (25%)	*c:* <0.001
ACT score				N.S.
23-27 (6-11 years)	69 (49%)			
23–25 (≥ 12 years)		58 (54%)	54 (26%)	
20–22	46 (33%)	22 (21%)	48 (23%)	
17–19	15 (11%)	16 (15%)	35 (17%)	
14–16	6 (4%)	5 (5%)	26 (13%)	
11–13	2 (1%)	4 (4%)	21 (10%)	
8–10	0 (0%)	1 (1%)	13 (6%)	
5–7	2 (1%)	1 (1%)	9 (4%)	
FEV_1% predicted	96 (IQR: 89–102%)	89 (IQR: 82–100%)	77 (IQR: 76–92%)	*a:* 0.011 *b:* <0.001 *c:* <0.001
Medications				
SABA	68 (49%)	54 (51%)	157 (76%)	*a:* 0.011 *b:* <0.001 *c:* <0.001
ICS intake	47 (34%)	49 (46%)	195 (95%)	*a:* N.S.
Low	37 (26%)	21 (20%)	51 (25%)	*b:* <0.001
Medium	13 (9%)	4 (4%)	32 (16%)	*c:* <0.001
High	56 (40%)	51 (48%)	107 (52%)	
LABA intake	–	–	170 (83%)	–
LAMA[1]	17 (12%)	13 (12%)	51 (25%)	*a:* N.S. *b:* <0.001 *c:* <0.001
LTRA	1 (1%)	3 (3%)	30 (15%)	N.S.

Biologicals	9 (6%)	3 (3%)	14 (7%)	*a:* N.S. *b:* 0.042 *c:* N.S.
Systemic steroids	9 (6%)	3 (3%)	45 (22%)	*a:* N.S. *b:* <0.001 *c:* <0.001
Theophylline			15 (7%)	–
Exacerbations				*a:* N.S.
Severe exacerbation (yes)	28 (20%)	18 (17%)	116 (56%)	*b:* <0.001 *c:* <0.001
Hospitalization (yes)	18 (13%)	13 (12%)	42 (20%)	N.S.

Values are given as median (interquartile range) for continuous variables, and absolute and relative frequencies for categorical variables, unless stated otherwise. LAMA intake was not recorded in children. *a:* Children 6–11 years vs. children 12–18 years; *b:* Children 6–11 years vs. adults; *c:* Children 12–18 years vs. adults.
ASSESS: Asthma Severity Scoring System; ICS: Inhaled Corticosteroids; IQR: Interquartile range; LABA: Long-acting beta agonist; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonist; N.S.: Not significant; SABA: Short-acting beta agonist; SD: Standard deviation

Table 3: ASSESS score distributions in pediatric and adult asthma patients at baseline and 12 months follow-up.

	ASSESS score (Baseline)	ASSESS score (12 months follow-up)
Children 6-11 years (n=140)	3.9 (2.6)	3.3 (2.4)
Children 12–18 years (n=107)	3.9 (3.2)	3.3 (2.9)
Adult Cohort (n=206)	8.5 (4.4)	5.7 (3.1)

Mean ASSESS score (SD) per age group.

Table 4A: Known-group validity – comparison between dichotomized outcome groups in children aged 6 – 11 years

Comparison in	**Outcome**	**Number of patients with outcome (%)**	**ASSESS score/ ASSESS score change**		**p-value**
			Subjects with outcome	Subjects without outcome	
Mean ASSESS score	≥1 exacerbation	28 (20%)	7.3 (2.0)	3.1 (2.0)	<0.001
	≥2 exacerbations	17 (12%)	7.2 (2.4)	3.5 (2.4)	<0.001
	≥1 hospitalization	18 (13%)	7.9 (2.3)	3.4 (2.1)	<0.001
	≥1 emergency doctor visit	51 (37%)	5.3 (2.7)	3.2 (2.3)	<0.001
	≥1 hospital stay with oxygen requirement	14 (10%)	8.5 (1.7)	3.4 (2.2)	<0.001
	≥2 wheeze episodes	61 (45%)	4.5 (2.7)	3.4 (2.5)	0.026
Mean ASSESS score change	≥3 ACT score increase	23 (26%)	-2.6 (2.8)	0.0 (2.1)	<0.001
	≥10% FEV_1% pred. increase	12 (13%)	-1.2 (2.6)	-0.6 (2.6)	0.330

Table 4B: Known-group validity – comparison between dichotomized outcome groups in children 12 – 18 years

Comparison in	**Outcome**	**Number of patients**	**ASSESS score/ ASSESS score change**	**p-value**

		with outcome (%)	Subjects with outcome	Subjects without outcome	
Mean ASSESS score	≥1 exacerbation	18 (17%)	8.6 (3.5)	3.0 (2.2)	<0.001
	≥2 exacerbations	11 (10%)	8.6 (3.0)	3.1 (2.4)	<0.001
	≥1 hospitalization	13 (12%)	7.1 (4.9)	3.5 (2.7)	0.003
	≥1 emergency doctor visit	25 (23%)	5.6 (4.3)	3.4 (2.6)	0.008
	≥1 hospital stay with oxygen requirement	11 (10%)	7.8 (3.5)	3.5 (2.7)	<0.001
	≥2 wheeze episodes	41 (40%)	5.6 (3.7)	2.5 (1.9)	<0.001
Mean ASSESS score change	≥3 ACT score increase	21 (27%)	-2.1 (2.0)	-0.5 (1.9)	0.001
	≥10% FEV_1% pred. increase	9 (11%)	0 (2.0)	-1.0 (2.0)	0.176

Table 4C: Known-group validity – comparison between dichotomized outcome categories (adults)

Comparison in	**Outcome**	**Number of patients with outcome (%)**	**ASSESS score/ ASSESS score change**		**p-value**
			Subjects with outcome	Subjects without outcome	
Mean ASSESS score	≥1 exacerbation	116 (56%)	11.1 (3.9)	5.3 (2.6)	<0.001
	≥2 exacerbations	43 (21%)	7.7 (3.4)	4.5 (2.1)	<0.001
	≥1 hospitalization	41 (20%)	13.0 (4.2)	7.5 (3.7)	<0.001
Mean ASSESS score change	≥3 ACT points increase	26 (25%)	-3.6 (2.6)	-0.6 (2.3)	<0.001
	≥10% FEV_1% pred. increase	10 (9%)	-3.1 (2.3)	-1.2 (2.7)	0.030
	≥0.5 AQLQ score increase	60 (61%)	-1.9 (2.7)	-0.6 (2.7)	0.027

Comparison between dichotomized outcome categories. The tables show for both pediatric cohorts (4A-B) and adults (4C) the mean ASSESS score in patients with and without specific outcomes (≥ 1 of 2 exacerbations, ≥ 1 hospitalization and ≥ 2 wheeze episodes (children only)) in the past 12 months. Additionally, the mean ASSESS score change between baseline and 12-months follow-up was calculated for patients with and without specific outcomes (increase of ≥ 3 points of the ACT, increase of ≥ 10% FEV_1 %predicted and ≥0.5 points increase of AQLQ score in adults only). P-values were calculated using Mann-Whitney *U* Test. ACT: Asthma Control Test; ASSESS: Asthma Severity Scoring System; FEV_1: Forced Expiratory Volume in 1 second, AQLQ: Asthma Quality of Life Questionnaire.

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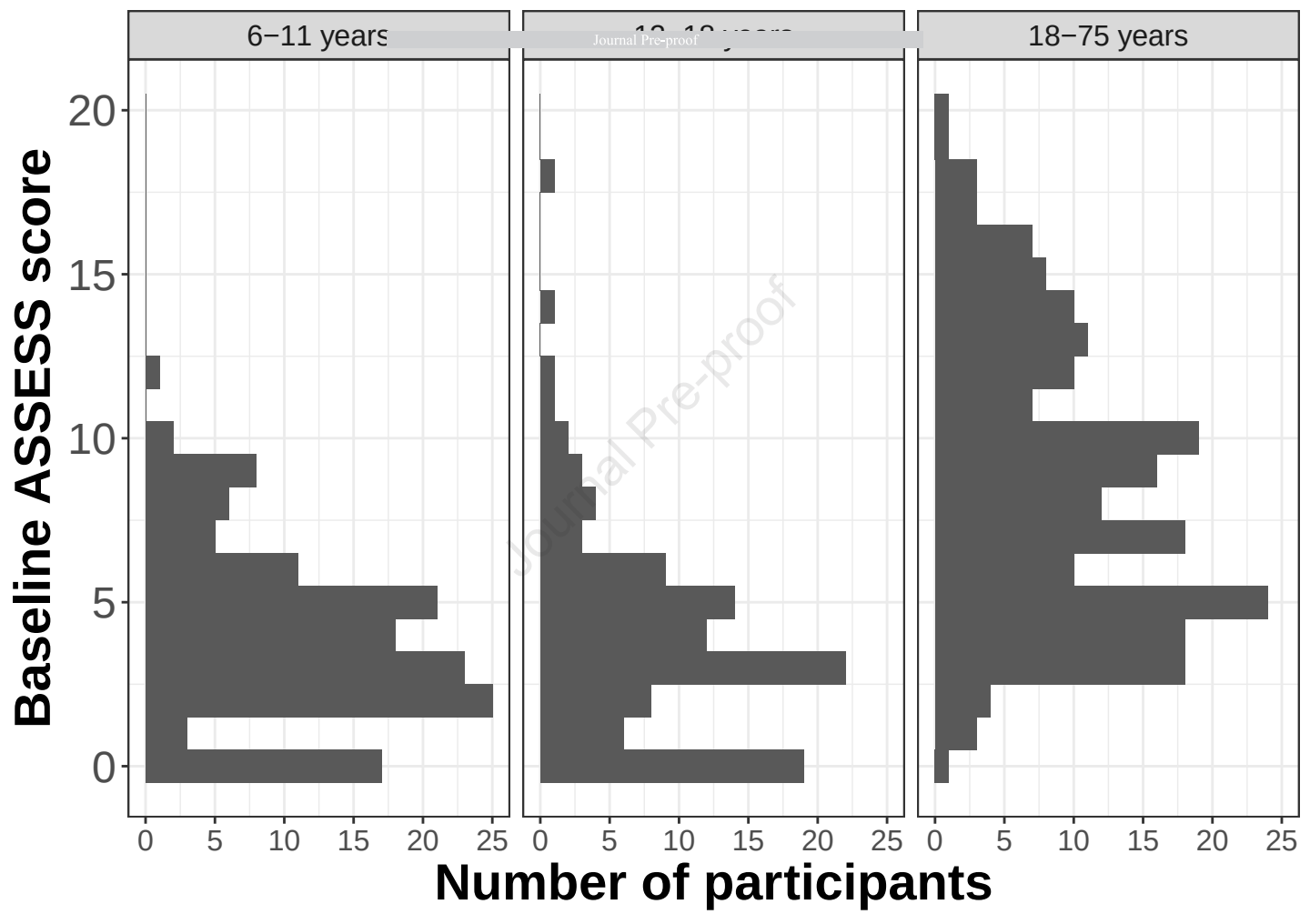
6–11 years
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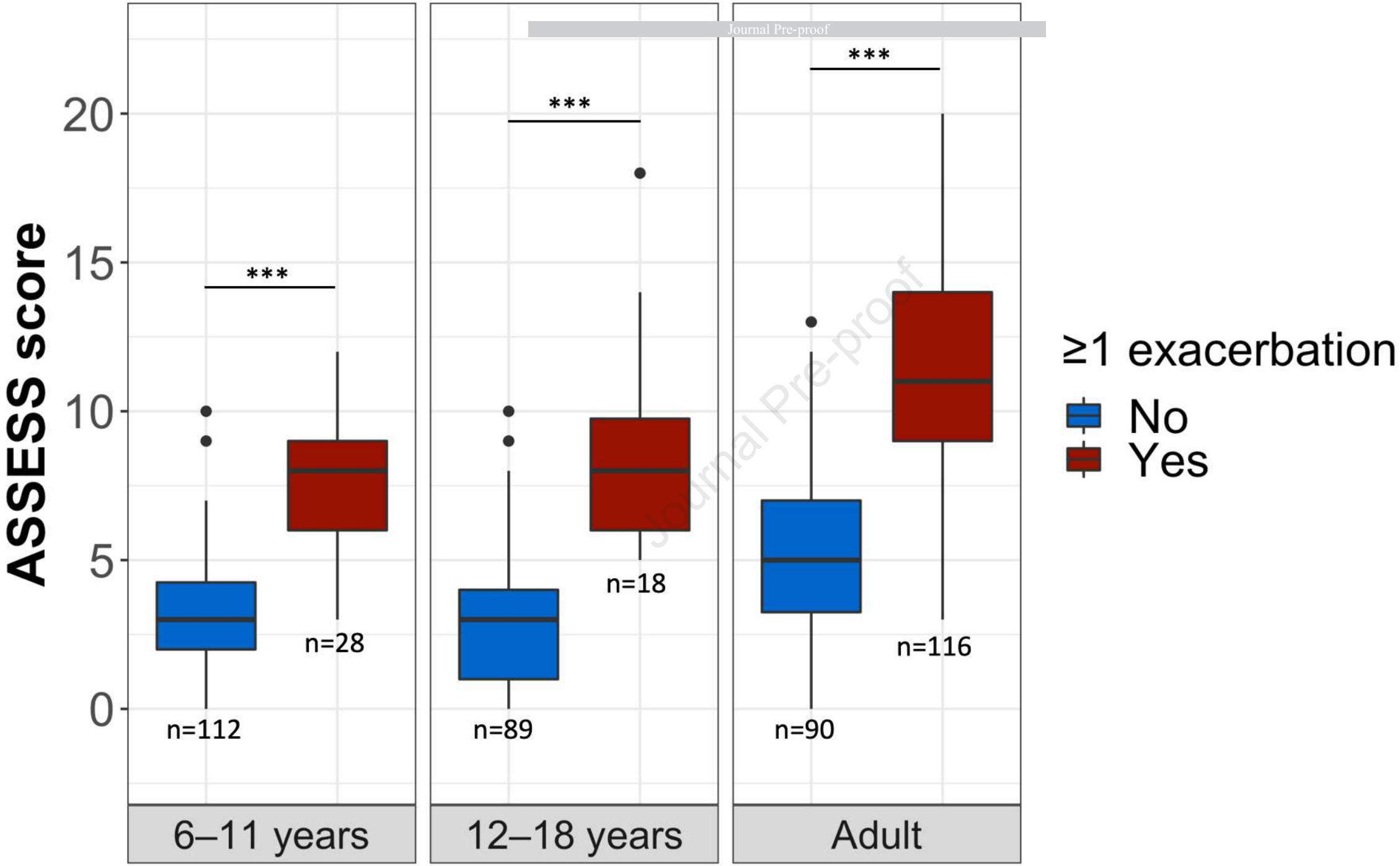

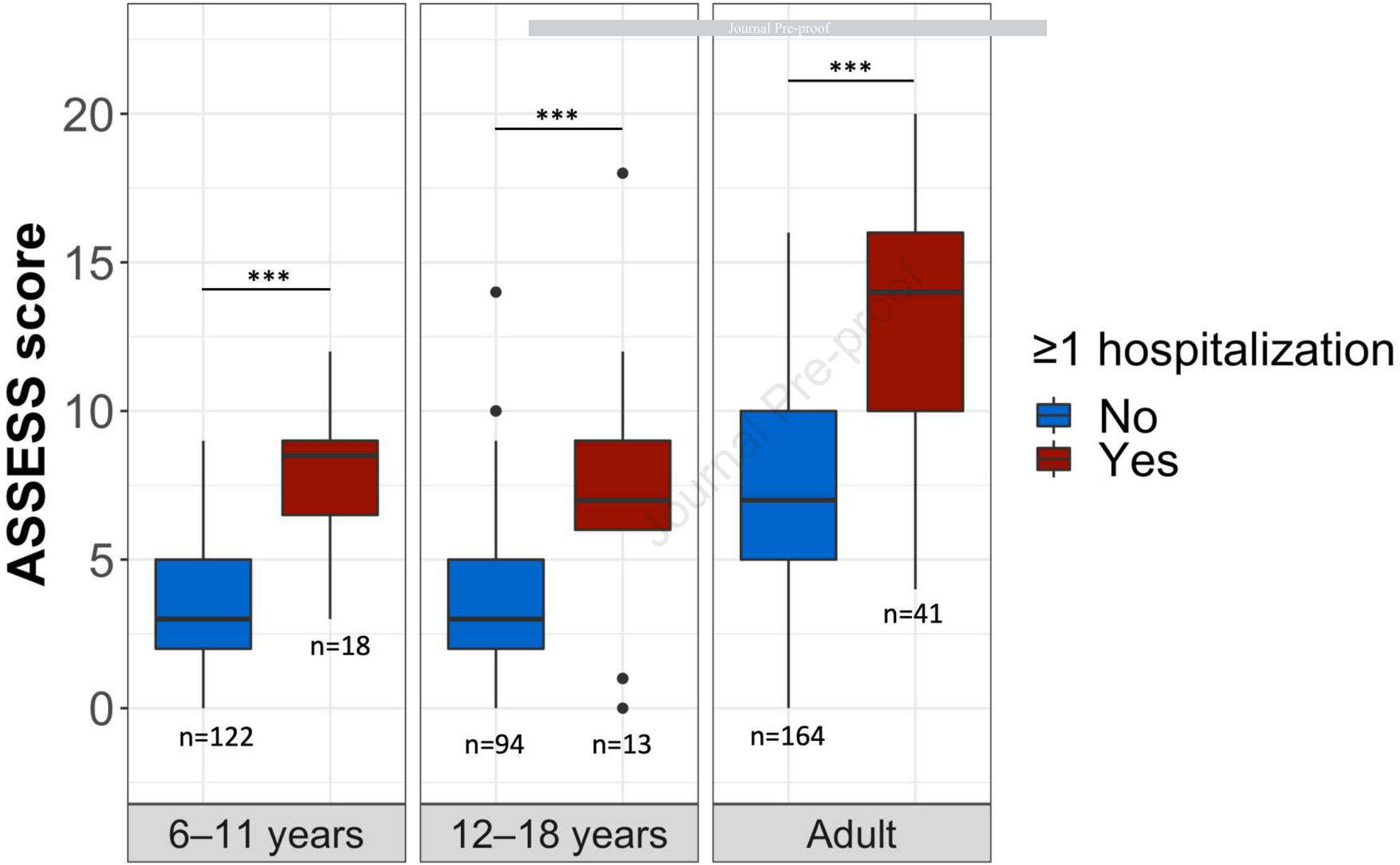

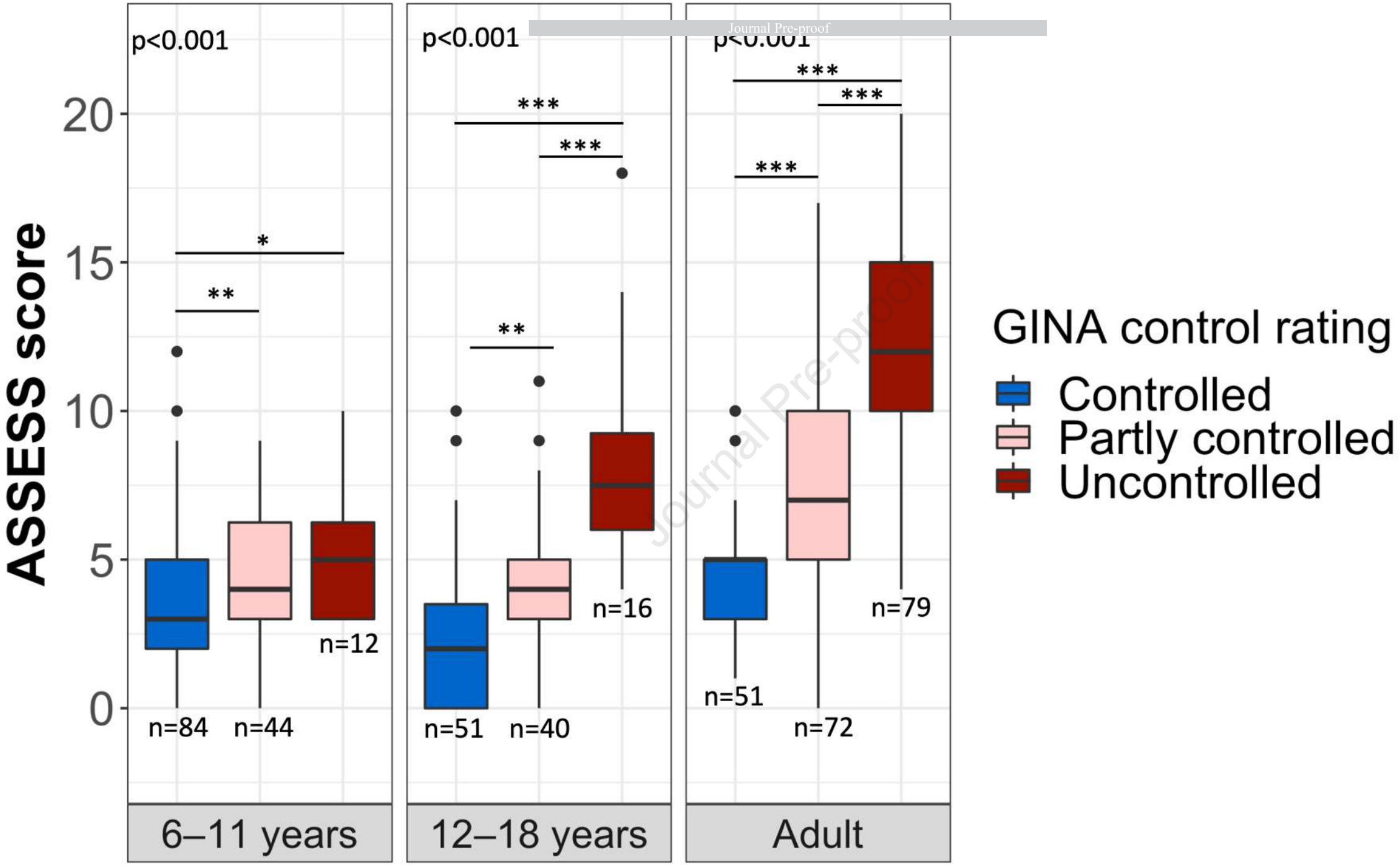

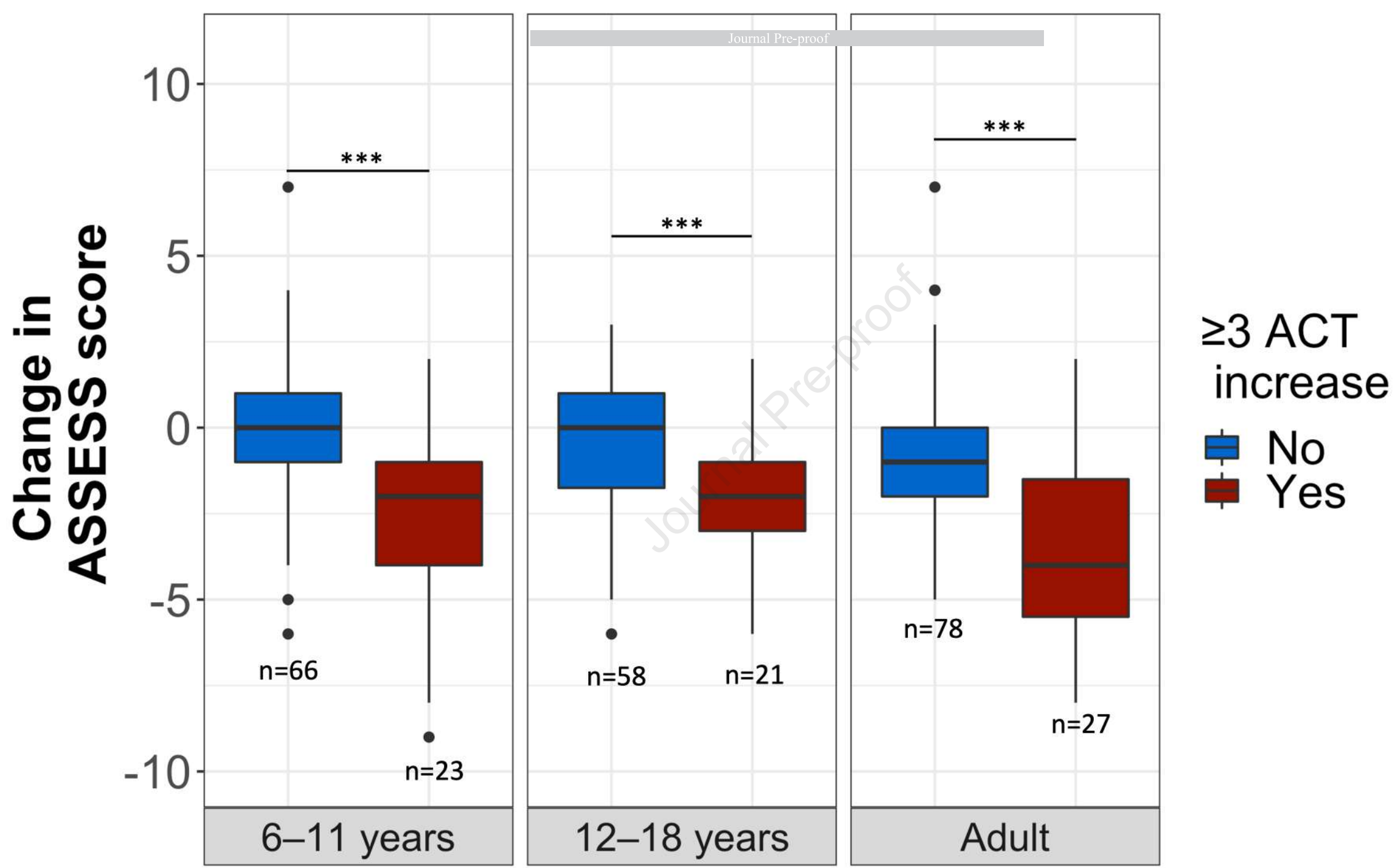

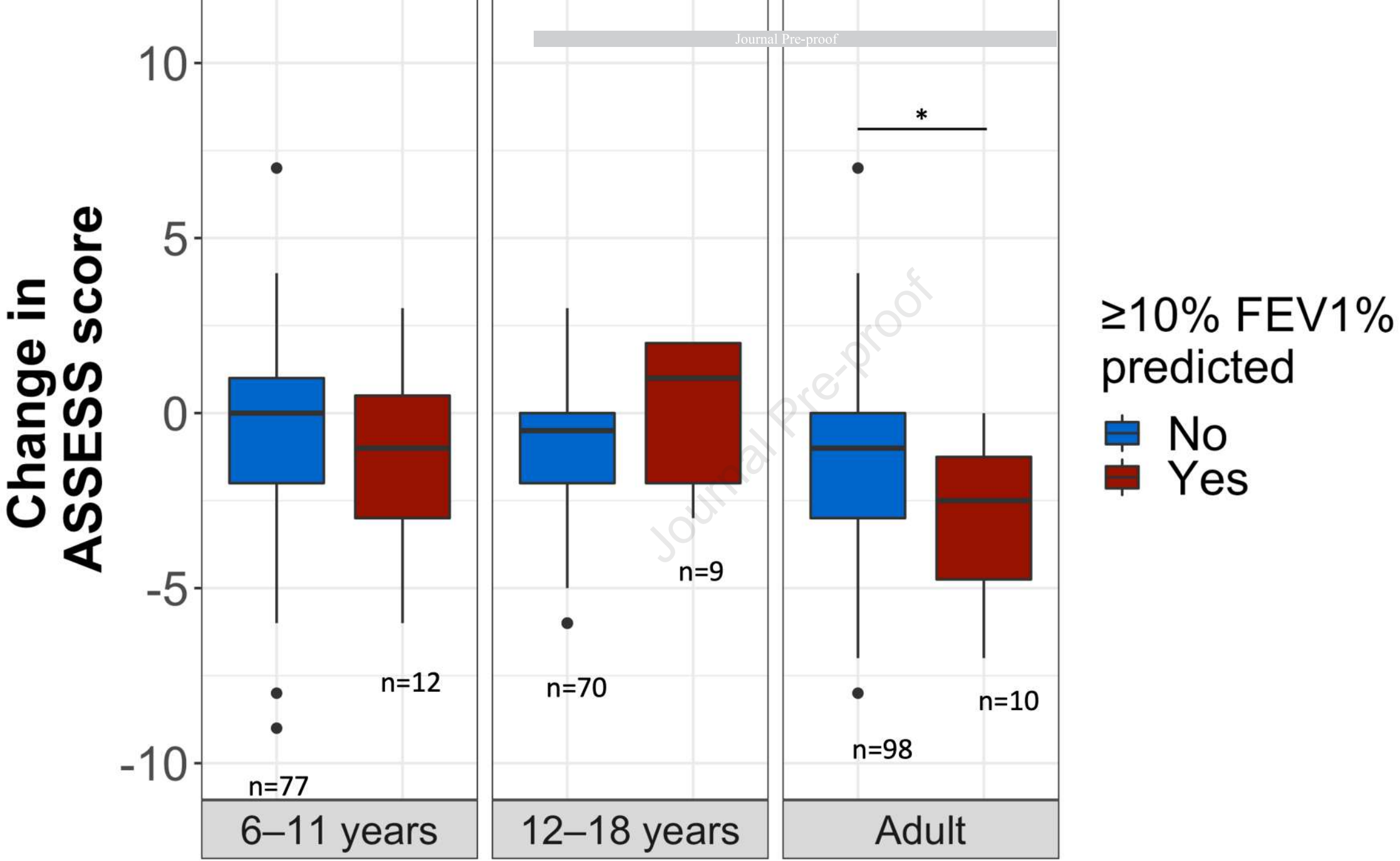

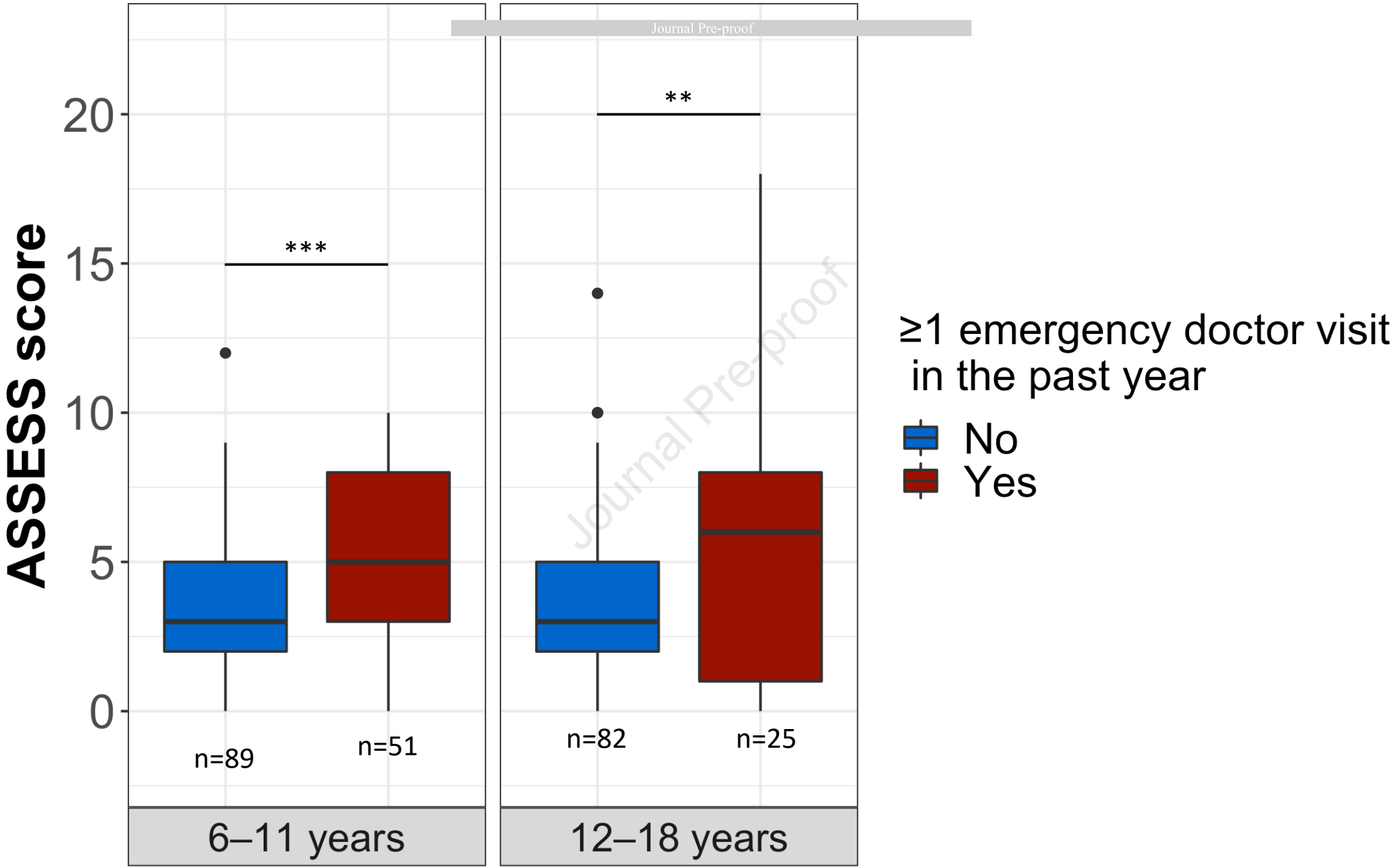

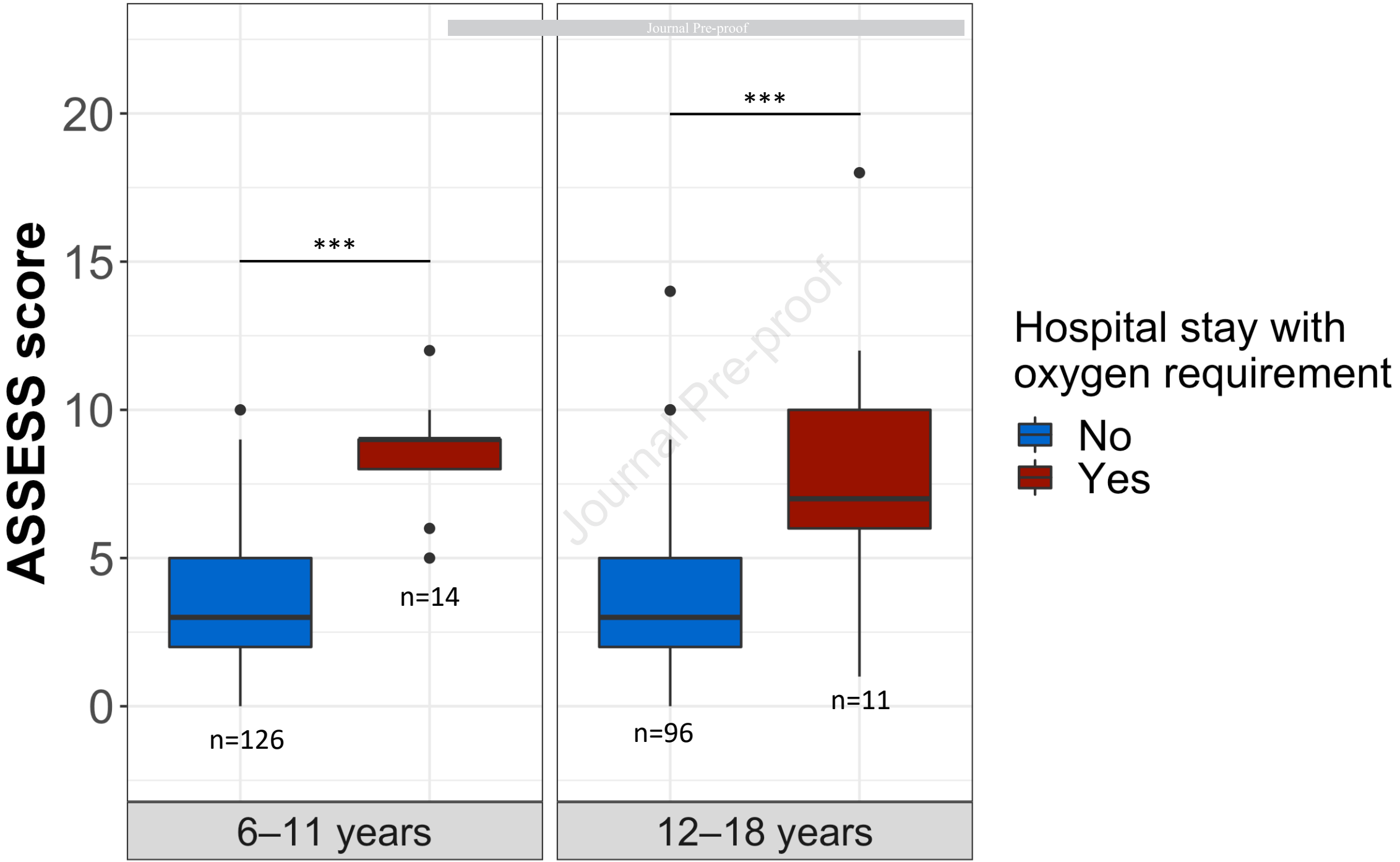

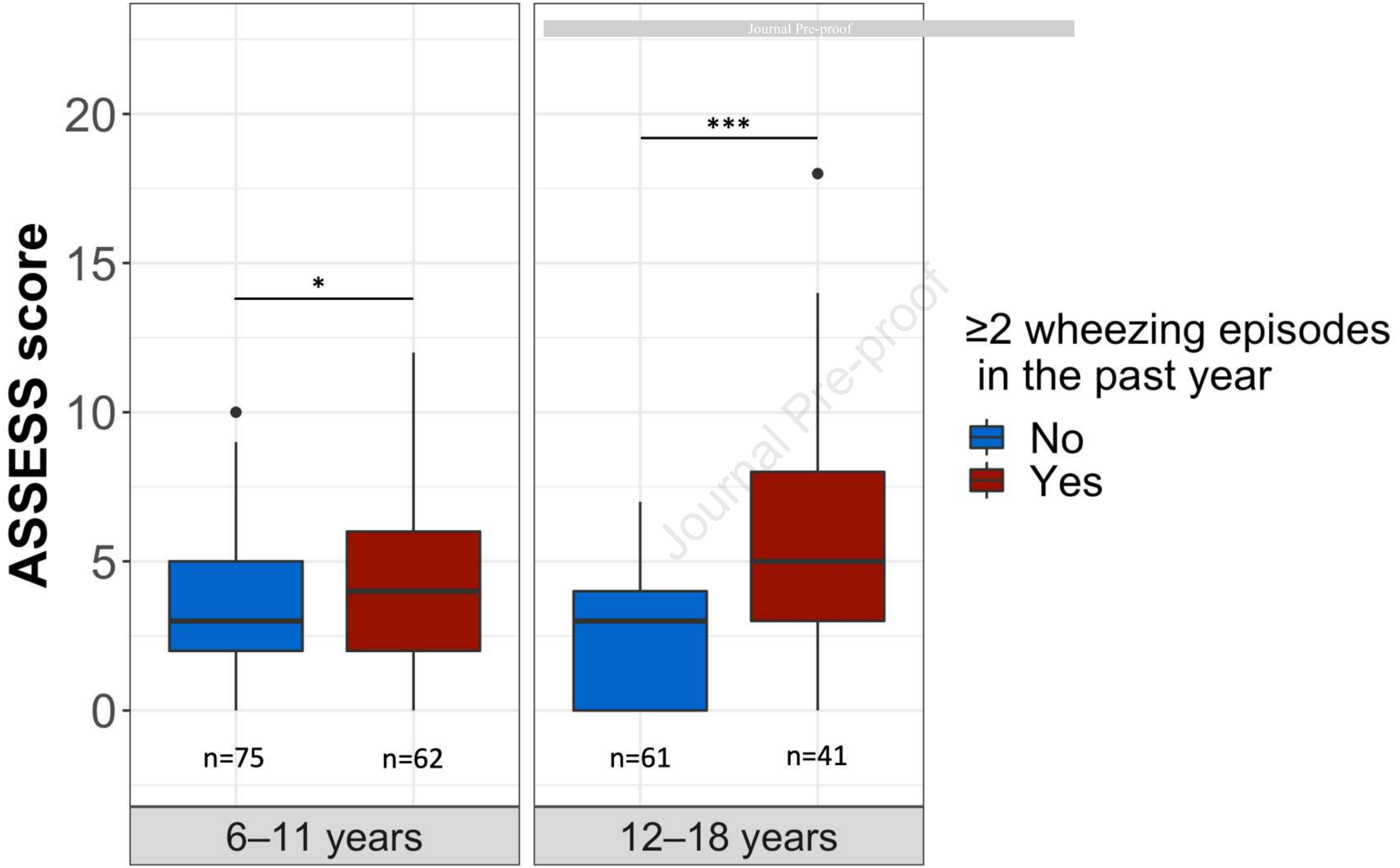

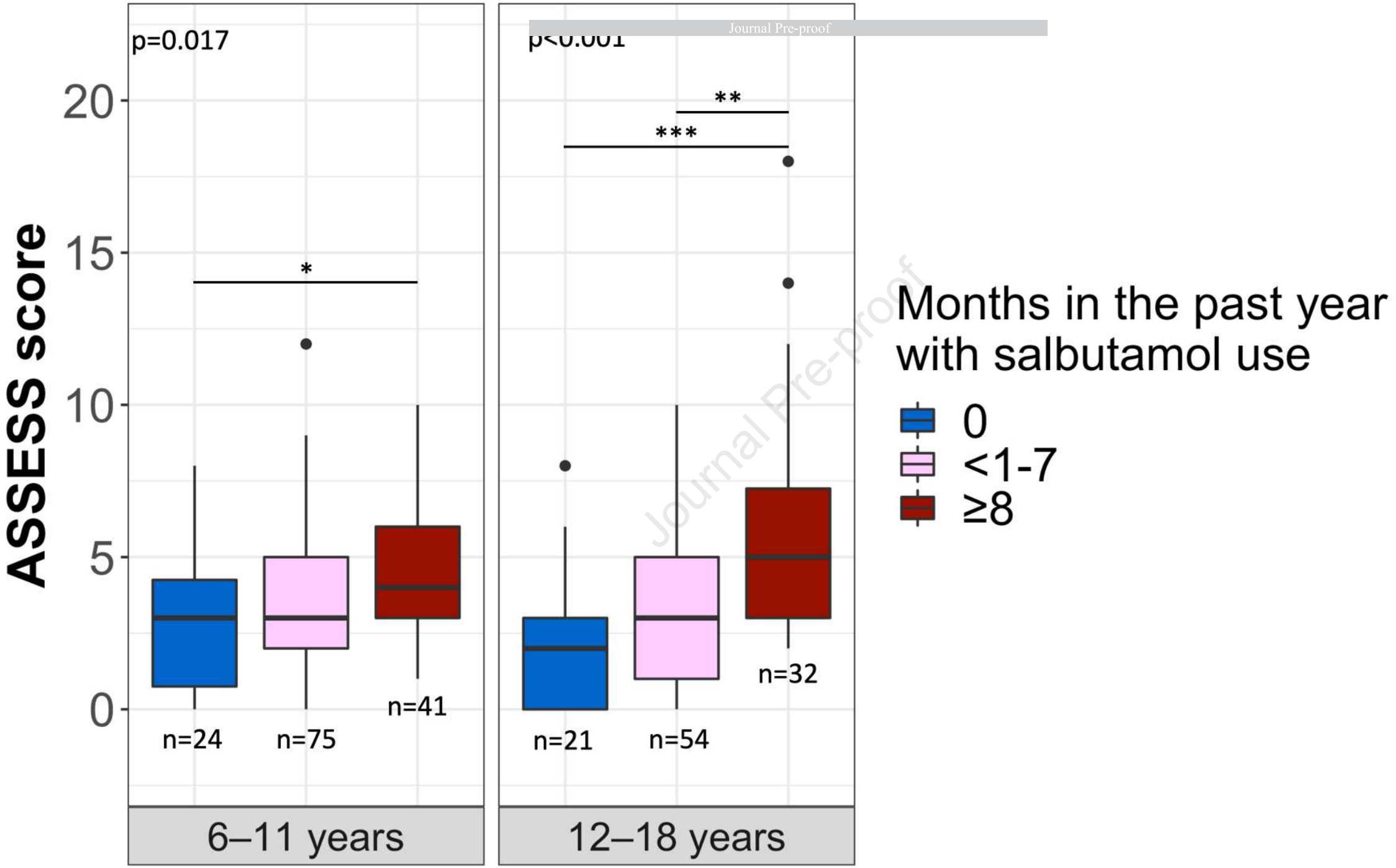

ALLIANCE COHORT PUBLICATION GUIDELINES Appendix I

Version V 4.2 Juli 2021

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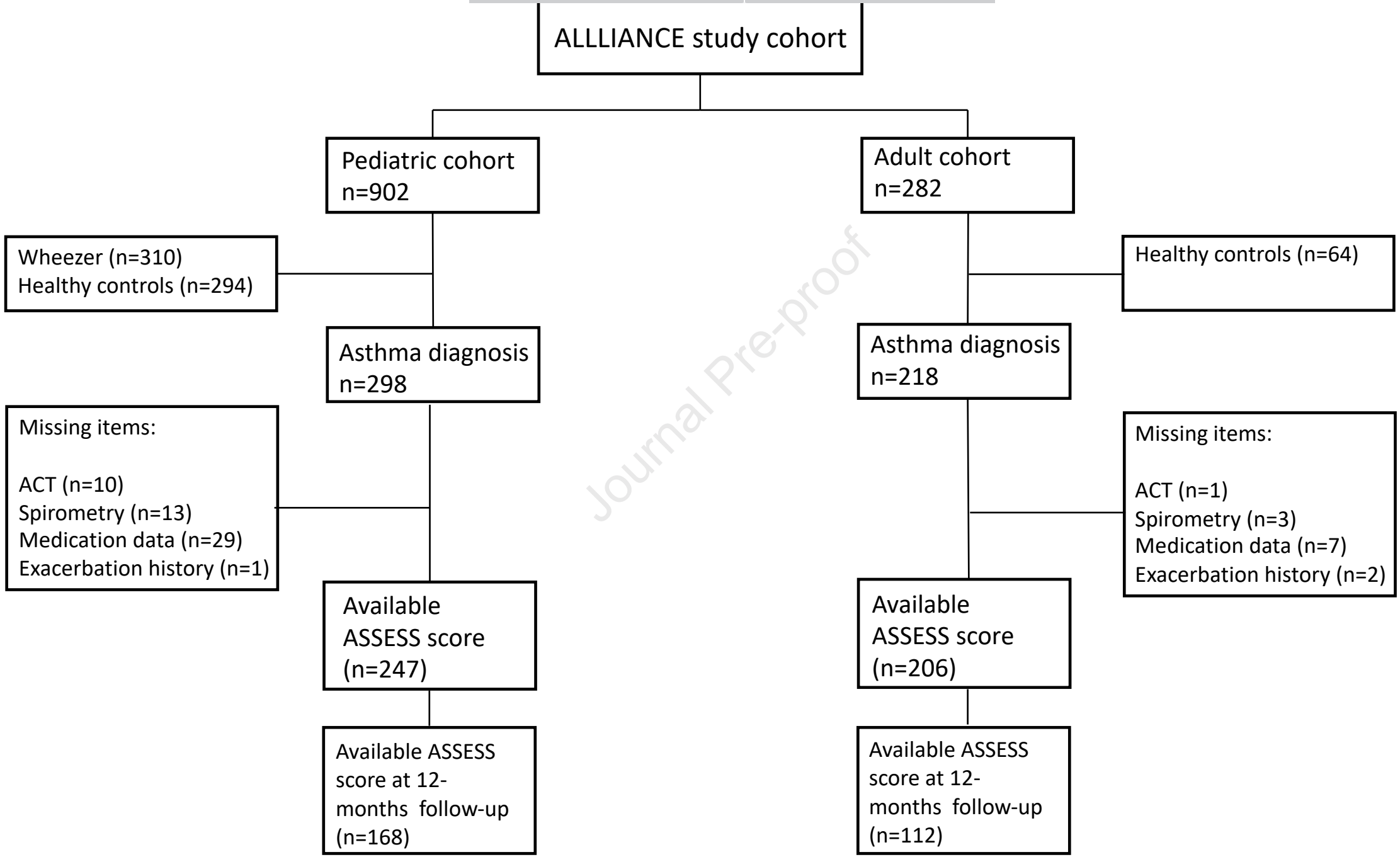

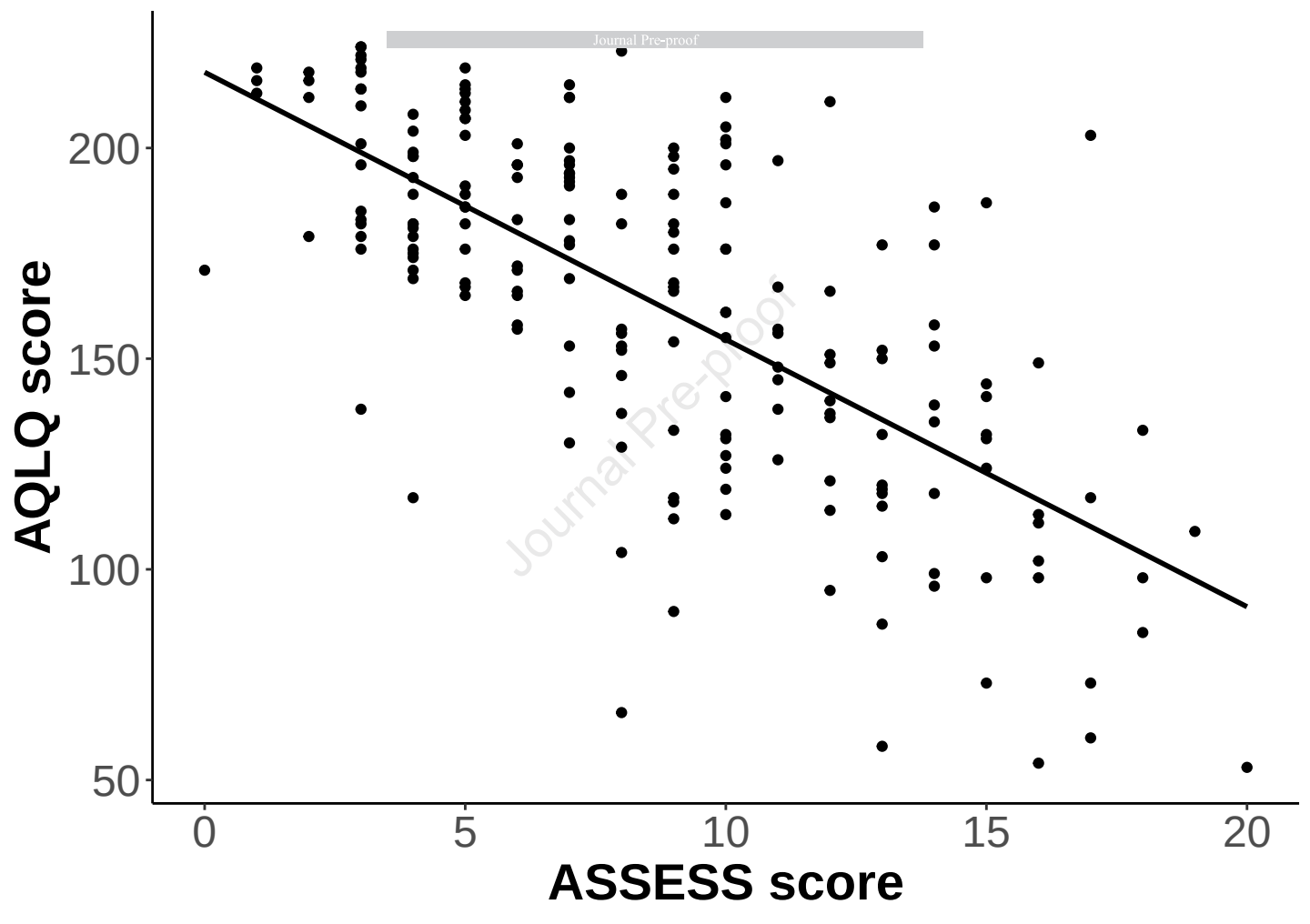

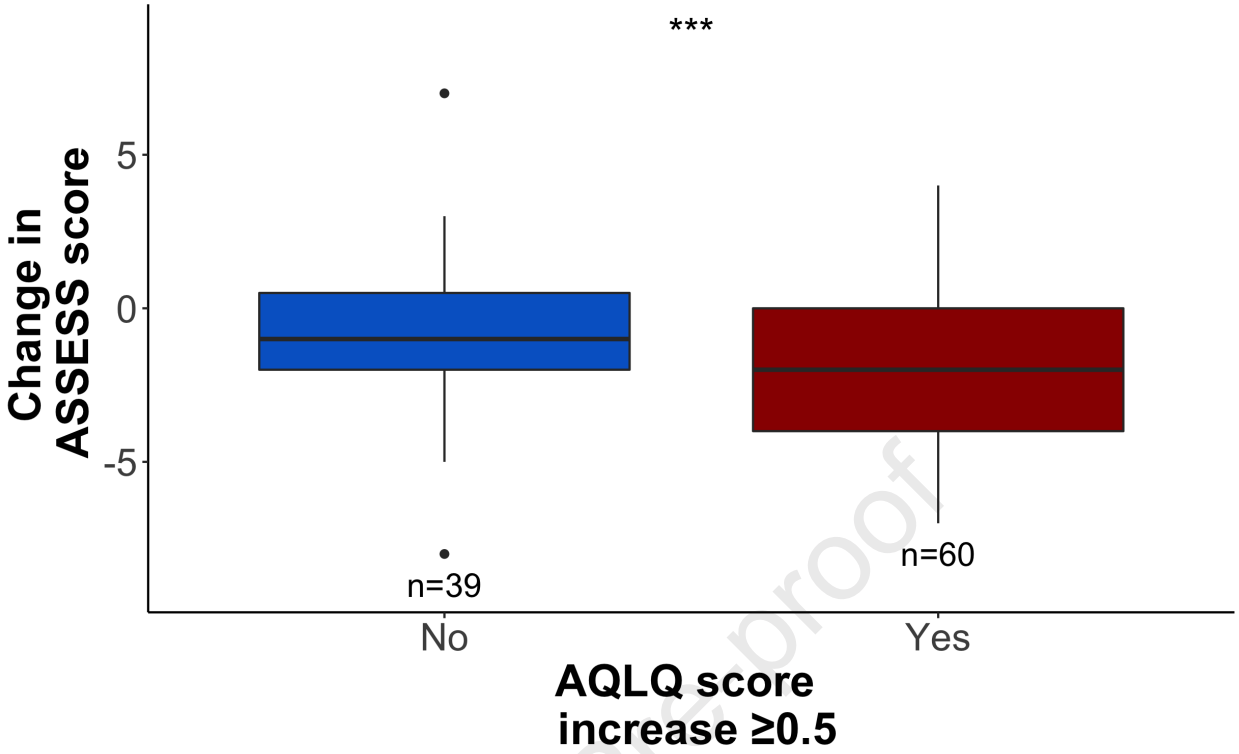

Application and External Validation of the Asthma Severity Scoring System (ASSESS) in children and adults

Online Repository

Supplemental Methods:

Study design:

Recruiting centres of the ALLIANCE cohort are five academic paediatric specialist centers (Hannover, Lubeck, Munich, Marburg and Cologne) and two adult specialist centers (LungenClinic Grosshansdorf and Research Centre Borstel).

Exacerbations were defined as worsening of asthma symptoms requiring systemic corticosteroid treatment (children: any length of systemic corticosteroid treatment, adults: at least 3 days of systemic corticosteroid treatment or up-titration of regular oral corticosteroid treatment). Wheeze episodes in children were defined as salbutamol treatment for more than two out of seven days. Asthma control was measured using the Asthma control test[1] and asthma control test for children[2] and according to GINA guideline 2014[3]. Salbutamol use in the past 12 months was recorded as a categorical variable (none, <1 month, 2-4 months, 5-7 months, 8-10 months, and 11 or more months). For analyses in this study, salbutamol use was grouped to none, 1-7 months, and 8 or more months to achieve sufficient sample numbers in each group.

The following dataset versions were used for the analysis: V5-0 (children) and baseline version 2021-02-10 and follow-up version 2021-02-15 (adults).

ASSESS score calculation:

In children aged <12 years, the Childhood ACT was used which adds to a total sum of 27 points, while in adults and children ≥ 12 years the total sum is 25 points. Accordingly, in children 6-11 years, having an ACT of 24-27 results in 0 points for the ASSESS score and an ACT of 20-23 in 1 point, while in children ≥ 12 years and adults the equivalent cut-offs are 23-25 points (0 points in the ASSESS score) and 20-22 points (1 point in the ASSESS score).

In ALLIANCE, “recent” medications (i.e., use in the past 4 weeks) were documented for each study visit, instead of “current” medications used in the original publication. Furthermore,

prednisone bursts and hospitalizations were recorded for the past 12 months the ALLIANCE cohort, which differs from the original publication, in which the past 6 months were considered.

Literature:

1. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004; 113:59-65.
2. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007; 119:817-25.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2014. Available from: www.ginasthma.org [cited 16-7-2019].

Supplement Figure Legends:

Figure E1: Study flow chart
Flow-chart illustrating the study design and included patients.

Figure E2: ASSESS score and quality of life in adults
Spearman correlation between AQLQ and ASSESS score at baseline in adult patients with asthma (2A). Change of ASSESS score between baseline and 12-months follow-up was compared in patients with clinical improvement of asthma-related quality of life (AQLQ score increase ≥0.5 points). Mann-Whitney *U* test (* $p < 0.05$).
AQLQ: Asthma Quality of Life Questionnaire, ASSESS: Asthma Severity Scoring System

Table E1: Cronbach`s alpha according to age groups

Table E1A: Pediatric cohort (6-18 years):

Cronbach's alpha	Item	Corrected Item-Total Correlation	Cronbach's alpha if item deleted
0.47 (0.37–0.56)	ACT score	0.58	0.23
	Lung function	0.20	0.47
	Medications	0.44	0.37
	Exacerbations	0.36	0.39

Table E1B: Adults:

Cronbach's alpha	Item	Corrected Item-Total Correlation	Cronbach's alpha if item deleted
0.73 (0.67–0.79)	ACT score	0.66	0.64
	Lung function	0.52	0.71
	Medications	0.66	0.64
	Exacerbations	0.60	0.67

Table E1C: Children 6–11 years:

Cronbach's alpha	Item	Corrected Item-Total Correlation	Cronbach's alpha if item deleted
0.27 (0.07–0.47)	ACT score	0.50	0.08
	Lung function	-0.18	0.36
	Medications	0.27	0.21
	Exacerbations	0.35	0.15

Table E1D: Children ≥ 12 years:

Cronbach's alpha	Item	Corrected Item-Total Correlation	Cronbach's alpha if item deleted
0.59 (0.47–0.70)	ACT score	0.69	0.37
	Lung function	0.40	0.57
	Medications	0.57	0.53
	Exacerbations	0.44	0.56

Table E1A-D:
The tables show Cronbach's alpha, corrected Item-total correlation and Cronbach's alpha if each included item is removed from the calculation. Data is shown for all children with asthma

aged 6-18 years (n= 247) (S2A), adults (n=206) (S2B), as well as children aged 6-11 years (n=140) (S2C) and children aged ≥ 12 years (n=107) (S2D).