

Received Date : 06-Oct-2015

Revised Date : 18-Mar-2016

Accepted Date : 25-Mar-2016

Article type : Original

**Title:** Development of a nomogram to estimate the Quality of Life (QoL) in asthmatic children by using the Childhood Asthma Control Test (C-ACT).

**Laura Montalbano, MSc<sup>1,2</sup>** (coprimary author), **Giovanna Cilluffo, MSc<sup>1,3</sup>** (coprimary author), **Manuel Gentile, D.Eng.<sup>4</sup>**, **Giuliana Ferrante, MD<sup>5</sup>, PhD**, **Velia Malizia, MD<sup>1</sup>**, **Fabio Cibella, MD<sup>1</sup>**, **Giovanni Viegi, MD<sup>1,6</sup>**, **Giovanni Passalacqua, MD<sup>7</sup>**, **Stefania La Grutta, MD, PhD<sup>1</sup>**.

National Research Council of Italy, Institute of Biomedicine and Molecular Immunology, Palermo, Italy<sup>(1)</sup>; Department of Psychological Educational and Training Sciences, University of Palermo, Italy<sup>(2)</sup>; Department of Economic, Business and Statistical Sciences, University of Palermo, Italy<sup>(3)</sup>; National Research Council, Institute for Educational Technologies, Palermo, Italy<sup>(4)</sup>; Department of Science for Health promotion and Mother and Child care, University of Palermo, Italy<sup>(5)</sup>; National Research Council of Italy, Institute of Clinical Physiology, Pulmonary Environmental Epidemiology Unit, Pisa, Italy<sup>(6)</sup>, Allergy and Respiratory Diseases, IRCCS San Martino-IST-University of Genoa<sup>(7)</sup>

**Running title:** Nomogram for quality of life in asthmatic children

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12571

This article is protected by copyright. All rights reserved.

Name, address and e-mail address of the author responsible for correspondence:

Stefania La Grutta, MD, PhD

National Research Council of Italy – Institute of Biomedicine and Molecular Immunology “A.

Monroy”

Via Ugo La Malfa, 153 90146 Palermo - Italy

Phone: +39 091 6809680 Fax: +39 091 6809122

E mail: stefania.lagrutta@ibim.cnr.it

### **Abstract page**

Authors' surnames and initials : Montalbano L.

Title of manuscript: Development of a nomogram to estimate the Quality of Life (QoL) in asthmatic children by using the Childhood Asthma Control Test (C-ACT).

Title of journal: Pediatric Allergy and Immunology

**Title:** Development of a nomogram to estimate the Quality of Life (QoL) in asthmatic children.

**Background:** Pediatric Asthma Quality of Life Questionnaire (PAQLQ) provides detailed information on QoL in asthmatic children whereas childhood Asthma Control Test (C-ACT) is the most validated instrument for asthma control. No study assessed the relationship between C-ACT and QoL in children by means of those instruments. Aim of the study was to determine whether a QoL estimation is possible using the C-ACT questionnaire in asthmatic children.

**Methods:** Medical history, spirometry, C-ACT and PAQLQ were assessed in 144 (60% male) outpatient asthmatic children from September 2011 to November 2014. A Generalized linear model (GLM) for prediction of PAQLQ was obtained through a stepwise procedure starting from a full model with all C-ACT item and predictive nomograms was created.

**Results:** 55 (38%) Well Controlled asthma (WC), 37 (26%) Partially Controlled (PC), and 52 (36%) Uncontrolled (UA) patients were enrolled. Persistent Asthmatics (PA) were significantly more uncontrolled ( $p<0.0001$ ). A significant reduction in  $FEV_1$ ,  $FEV_1/FVC$ ,  $FEF_{25-75}$  ( $p=0.005$ ,

This article is protected by copyright. All rights reserved.

$p < 0.0001$ ,  $p < 0.001$ , respectively) was found in WC vs UA. Through a stepwise process, a reduced model showed a positive relationship between the PAQLQ and the four items of C-ACT. The regression equations for predicted PAQLQ were  $\ln(\text{PAQLQ}) = 0.05 * \text{C-ACT2} + 0.03 * \text{C-ACT3} + 0.04 * \text{C-ACT6} + 0.03 * \text{C-ACT7}$ . Thus a nomogram was constructed.

**Conclusion:** The designed nomogram provides a highly predictive assessment of QoL in individual patients, facilitating a more comprehensive assessment of asthmatic children in usual clinical care.

Key words: children, asthma, nomogram, C-ACT, PAQLQ, control

## Introduction

Achieving and maintaining asthma control is the goal of asthma treatment according to GINA guidelines [1], and this keeps true also in children. Quality of Life (QoL) instruments represent an useful tool to better assess asthma control in children [2]. The Childhood Asthma Control Test (C-ACT) is a worldwide validated composite test to assess asthma control in children aged 4-11 years [3], and the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) is a supplemental validated instrument to quantify the child's emotional reactions to the symptoms and limitations caused by asthma, mainly related to health and functional status [4].

Both tools have limitations due to the compiler age (overestimation or underestimation of symptoms). In fact, the C-ACT accounts for this limitation, with part of the items completed by the parent [5]. In addition, the PAQLQ, that must be filled only by the children, is time-consuming due to the amount of items [6].

Previous studies focused on the association of poor asthma control and impaired QoL [7, 8]. Recently, other studies showed a close correlation between C-ACT and PAQLQ [9], as well as between Asthma Control Questionnaire (ACQ) and PAQLQ [10]. In addition, the ability of either C-ACT total score or its individual questions for predicting clinical conditions, such as exercise

induced bronchoconstriction or nocturnal asthma, were reported [11], confirming that C-ACT is a valid complementary tool for predicting clinical outcome in asthmatic children [12].

A nomogram is a graphic tool that allows to predict outcome of interest, by means of a statistically-constructed model [13]. An advantage of nomogram over the conventional combined use of the C-ACT composite test and the supplemental tool is the predictive power of the outcome of interest (PAQLQ) captured in a single numerical value. Since asthma control is a multidimensional concept it would be of interest to integrate different measures into a single tool.

Aim of this study was to construct the Pediatric Asthma Control Quality of Life (PACQoL) nomogram using C-ACT test to estimate the predicted values of QoL in asthmatic children aged 5-11 years, allowing a multidimensional disease assessment in clinical practice by a single tool.

## **Methods**

This is a pilot study, part of the “Childhood Asthma and Environment Study (CHASER, clinicaltrials.gov NCT 02433275), an ongoing cross-sectional study at the Pediatric Allergology & Pulmonology outpatient clinic of IBIM CNR, Palermo, Italy. After parents or legal guardians were interviewed by medical well-trained investigators (S.L.G., V.M., G.F.) according to the SIDRIA (Italian Studies on Respiratory Disorders in Children and the Environment) questionnaire [14], the PAQLQ was filled by participants alone whilst C-ACT also by parents. The study was observational, did not involve experimental drugs or interventions, and was notified to the inner Ethical Committee. All the patients and their parents gave written informed consent before entering the study. The study was approved by the AOU Policlinico Paolo Giaccone Ethics Committee, Palermo, Italy.

### *Study population*

Over 299 children with asthma, aged between 5 and 11 years, referred from September 2011 to November 2014 for a planned visit at the Pediatric Allergology & Pulmonology outpatient clinic of IBIM CNR of Palermo, 224 (75%) correctly performed pre and post bronchodilator spirometric maneuver; 144 (64%) of them correctly completed both C-ACT and PAQLQ. None of the patients were on drug treatment at the time of the enrollment nor were smokers. Exclusion criteria were pulmonary diseases other than asthma and inability to perform spirometry.

### *Definitions and classifications*

The definition of asthma severity and asthma control status (Well Controlled, WC; Partially Controlled, PC; Uncontrolled Asthma, UA) was retrospectively performed according to GINA (Global Initiative for Asthma) 2008 [1].

### *Childhood Asthma Control Test (C-ACT)*

The C-ACT includes seven items related to the previous 4 weeks, divided into two parts. One part is filled in by the interviewed children, properly supported by their caregiver when necessary, by four questions on the perception of asthma control (Q1), limitation of activities (Q2), coughing (Q3) and awakenings at night (Q4). Each question has four response options. The second part is filled in by the parent/caregiver and with three questions: daytime complaints (Q5), daytime wheezing (Q6) and awakenings at night (Q7). Each question has six response options. The sum of all scores yields the C-ACT score, ranging from 0 (poor asthma control) to 27 (optimal asthma control). A cut-off point of 19 indicates uncontrolled asthma [3].

### *Lung function*

Pulmonary function tests were performed through a portable spirometer (Pony FX portable spirometer, Cosmed, Rome, Italy). The patients performed a deep inhalation maneuver followed by a maximal expiratory maneuver, wearing a nose clip. These forced expiratory maneuvers were performed after a brief demonstration and training by well-trained physicians (S.L.G., V.M., G.F.). The tests were considered successful when three acceptable and reproducible curves were achieved. FVC, FEV<sub>1</sub>, and FEF<sub>25–75%</sub> were measured according to ATS/ERS guidelines: the best FVC and FEV<sub>1</sub> were retained, and FEF<sub>25–75%</sub> was selected from the maneuver with the largest sum of FEV<sub>1</sub> and FVC. The spirometric values were normalized as a percentage of the predicted values, in accordance with the values obtained by the reference equations described by the Global Lungs Initiative (GLI) [15]. A bronchodilator testing was performed: spirometry was repeated after a 15-min interval from the inhalation of 400 µg of salbutamol aerosol, using a spacer.

### *Quality of life*

Quality of life in asthmatic children was measured through the Italian version of PAQLQ [16].

PAQLQ includes 3 domains:

1. *Symptoms (S)*: questions 1, 3, 5, 7, 9, 11, 13, 15, 17, 20;
2. *Activity Limitations (AL)*: questions 16, 19, 21, 22, 23;
3. *Emotional Function (EF)*: questions 2, 4, 6, 8, 10, 12, 14, 18.

After receiving exhaustive explanations on questions and answering modalities, the children themselves filled out the questionnaire, properly supported by their caregiver when necessary. For each child, the overall score was calculated as the mean of the three domains. The scores ranged from 1 to 7, being 1 the minimum and 7 the maximum. The same approach was adopted for each subgroup of questions.

## *Statistical analysis*

Mean values were compared between GINA control groups using one-way analysis of variance (ANOVA). Differences of categorical variables between the GINA control groups were analyzed using Chi-squared test. Spearman correlations were applied for the relationships between C-ACT, PAQLQ and PAQLQ domains. Correlations were displayed in a correlation matrix plot. Through a Shapiro Wilk test, we checked the not normality of the response variable (PAQLQ). A Generalized Linear Model (GLM) with a log link and a Gamma family, due to the bounded nature of the response variable, was used for PAQLQ total score. The full model was composed by all C-ACT item. Parsimonious models were obtained by using a stepwise approach. The Akaike Information Criterion (AIC) was used as a measure to compare different models. A nomogram was derived to manually obtain predicted values from a regression model. The nomogram does not have lines representing sums, but it has a line called "Total points", ranged between 0 and 400, useful to locate predicted value of the response variable. The sum of the single score related to each explanatory variable composes the value to look for on "Total points" line. Once the reader obtain the "Total point" value, he can find the response predicted value through a perpendicular projection, connecting "Total points" line with "predicted value" line [17].

Analyses were performed using R 3.1.0 statistical analysis software. A  $p\text{-value} < 0.05$  was considered statistically significant.

## **Results**

### *Population*

The demographic characteristics of asthmatics subjects according to the level of asthma control are presented in Table 1. There were 55 (38%) Well Controlled (WC), 36 (26%) Partially Controlled (PC), and 52 (36%) Uncontrolled (UA) patients. Inadequate control was recorded for 88 (61%) children. Persistent Asthmatics (PA) were significantly more uncontrolled ( $p < 0.0001$ ). Significant trends of reduction in  $FEV_1$ ,  $FEV_1/FVC$ ,  $FEF_{25-75}$  ( $p = 0.005$ ,  $p < 0.0001$ ,  $p < 0.001$ , respectively). This article is protected by copyright. All rights reserved.

respectively) were found from WC to UA. A statistically significant trend in the number of exacerbations in the last 12 months was found in WC vs UA ( $p<0.0001$ ).

#### *Association between C-ACT and GINA asthma control*

A significantly different frequency distribution of C-ACT total score by level of GINA asthma control was found, that is a lower scores, according to the reduced control ( $p<0.001$ ) (Figure 1).

#### *Correlations*

Significant correlations between PAQLQ total score and PAQLQ AL ( $\rho=0.74$ ,  $p<0.001$ ), and between PAQLQ total score and PAQLQ S ( $\rho=0.82$ ,  $p<0.001$ ), and between PAQLQ total score and PAQLQ EF ( $\rho=0.83$ ,  $p<0.001$ ) were identified (Figure 2).

#### *Generalized linear model*

A generalized linear model with Gamma family and logarithmic link was applied in order to estimate the relationship between the PAQLQ and C-ACT. The starting point was a full model considering all C-ACT item:

$$\log(\text{PAQLQ}) = \beta_1 \text{CACT}_1 + \beta_2 \text{CACT}_2 + \beta_3 \text{CACT}_3 + \beta_4 \text{CACT}_4 + \beta_5 \text{CACT}_5 + \beta_6 \text{CACT}_6 + \beta_7 \text{CACT}_7$$

Through a stepwise process based on Akaike Information Criterion (AIC) a parsimonious model was found:

$$\log(\text{PAQLQ}) = \beta_1 \text{CACT}_2 + \beta_2 \text{CACT}_3 + \beta_3 \text{CACT}_6 + \beta_4 \text{CACT}_7$$

**Table 2** shows the estimates of the parsimonious model, there is a positive relationship between the outcome and the four items. If C-ACT<sub>2</sub> increases by one unit, PAQLQ increases in mean of 1.05 [ $\exp(0.05)$ ], when C-ACT<sub>3</sub> or C-ACT<sub>7</sub> increase by one unit PAQLQ increase in mean of 1.03 [ $\exp(0.03)$ ], finally increasing by one unit of C-ACT<sub>6</sub> implies an average increasing by 1.04 [ $\exp(0.04)$ ] of PAQLQ. No differences were found in models stratified by gender and asthma severity.

## Nomogram

The relationship observed in the parsimonious model has allowed to develop a nomogram for predicting PAQLQ values. Figure 3 shows the nomogram with all possible combinations of each C-ACT item. To obtain the predicted value of QoL the following steps are required: 1) each value of selected C-ACT items has to be reported on the *Points* line (0-100, each bar corresponds to 2.5 units) on the top of the figure; 2) the four obtained scores have to be summed each other; 3) the obtained sum has to be reported on the *Total Points* line (0-400, each bar corresponds to 10 units); 4) the *PAQLQ Predicted Value* will be obtained by tracing a perpendicular segment from the *Total Points* line to the *PAQLQ Predicted Value* line. An example and a table with all possible combinations is in the supplement (Table S1).

## Clinical test of the nomogram

Figure S1 plots the predicted values vs the observed values, dark points are the units misclassified, while gray points are correctly classified. About 70% of the units with our rule are correctly classified. No differences were found between the misclassified and the correctly classified groups of children in terms of age, gender, BMI, atopy, spirometry and other.

## Discussion

The assessment of asthma control and QoL are important aspects in children's asthma management. Since C-ACT and PAQLQ give valuable information about the disease's perception by children and parents, we developed an algorithm for asthma QoL through four selected C-ACT questions. Therefore, in our PACQoL nomogram C-ACT selected questions are able to predict QoL

C-ACT has been validated in children and extensively used in clinical trials [3, 18, 19] as reliable assessment tool for disease burden perception by patients. We also found significant association between the frequency distribution of C-ACT total score and the level of GINA asthma control. Asthma was uncontrolled in 61% of our children as found by others [20, 21].

The questionnaires on QoL in asthmatic children have some special features to be mentioned. Firstly, age is to be taken into account, since it has been shown that children older than 10 years are able to develop the concept of chronic disease and the impact that this will generate in their lives. However, in children under age 6 a difficulty for understanding abstract concepts related to emotional or social limitations is reported [22]. Secondly, the drawback of time consuming, given by the large number of items, might limit their usefulness in daily clinical practice by physicians [5].

In our model, we have observed that starting from a full GLM, in which all C-ACT items were considered, through a stepwise procedure, the PAQLQ significantly depended on only four C-ACT items.

Differently from Chinellato et al., who did not find a statistically significant relationship between the score related to the C-ACT 2 query on symptoms when running, exercising, or playing sports and the  $\Delta FEV_1$  response to the exercise test [11], in our study C-ACT 2 shows the highest weight for predicting PAQLQ. This result provides additional information on how much an individual's illness interferes with daily life and how well the patient is adapting to his or her illness across several areas of functioning such as social, emotional, and physical.

The relationship between asthma severity and child QoL is not well established. Some authors reported that poorly controlled asthma is not consistently associated with measurements of child QoL [23, 24], whereas others found a strong correlation with symptoms of poorer control [25]

This article is protected by copyright. All rights reserved.

or with morbidity in adolescents and in children younger than 11 years, respectively [26]. Our findings are consistent with Okelo et al., who have observed that the PAQLQ is responsive to changes in asthma status within and between individual asthmatic children with varying severity of asthma [27].

In our analysis the parsimonious GLM model shows a positive relationship between the PAQLQ and the C-ACT four items, independently from gender and asthma severity. These findings are supported by previous [28] and more recent data [8, 29] suggesting that a child whose asthma symptoms are not well controlled might experience larger impairment in QOL. Thus, asking young children and their parents specific questions about their symptoms elicits valid and important information about their experience, which can help assessing their asthma control.

This is the first published nomogram for PAQLQ concerning asthmatic children. The PACQoL nomogram is a tool that provides a forecast of PAQLQ burden for an individual asthmatic child. It could be more easily applied than a more time consuming PAQLQ in a field investigation and also in clinical practice. Although several algorithms for asthma diagnosis [30] and for predicted PEFR [13] have been previously developed, our PACQoL nomogram could improve the overall clinical assessment of asthma control by physicians, responding to the need of guidelines recommendation.

Beside the advantage of the nomogram derivation, several potential limitations need to be considered in this study. First, variables were obtained from children aged 5 to 11 years; therefore, the nomogram may not be generalizable to older individuals and requires validation in other groups of asthmatic children. The sample size is relatively small, although there is detailed information on all study participants, including confirmation of the diagnosis of asthma based on clinical symptoms and test of reversibility. Finally, the PACQoL nomogram returns an overall idea about QoL without information about the single domains explored by PAQLQ. However, having found a strong relationship between C-ACT and PAQLQ, it is possible to state that our nomogram is able to provide very reliable information about QoL.

## Conclusion

We developed a model in order to predict the QoL starting from questions of C-ACT. Although this model requires validation in other clinical study, it is potentially useful in clinical practice in case in which the time is bounded or in case in which the available information concern only the asthma control. Therefore, this PACQoL nomogram may help physicians to better address the multidimensional construct of asthma in children.

Future research should focus on validation of the model in the same population during the planned second follow-up of this cohort.

## Acknowledgements

We thank all the parents and children who made possible the study.

## References

1. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;**31**:143–78
2. Braido F, Bousquet PJ, Brzoza Z, et al. Specific recommendations for PROs and HRQoL assessment in allergic rhinitis and/or asthma: GA<sup>2</sup>LEN task force position paper. *Allergy* 2010;**65**:959-968.
3. Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol*. 2007;**119**:817–825.
4. Wilson SR, Rand CS, Cabana MD, Foggs MB, Halterman JS, Olson L, et al. Asthma outcomes: Quality of life. *J Allergy Clin Immunol*. 2012;**129**:S88-123.
5. Shefer G, Donchin M, Manor O, Levy-Hevroni R, Schechter A, Cohen R, et al. Disparities in assessments of asthma control between children, parents, and physicians. *Pediatric Pulmonology*. 2014;**49**:943–951.

6. Brand PLP, Mäkelä MJ, Szeffler SJ, Frischer T, Price D, On behalf of the ERS Task Force Monitoring Asthma in Children. Monitoring asthma in childhood: symptoms, exacerbations and quality of life. *Eur Respir Rev.* 2015;**24**:187–193.
7. Guilbert TW, Garris C, Jhingram P, Bonafede M, Tomaszewski KJ, Bonus T, et al. Asthma that is not well-controlled is associated with increased healthcare utilization and decreased quality of life. *Journal of Asthma* 2011;**48**:126-132.
8. Schmier JK, Manjunath R, Michael T. Halpern MT, Mechelle L. Jones ML, et al. The impact of inadequately controlled asthma in urban children on quality of life and productivity. *Ann Allergy Asthma Immunol.* 2007;**98**:245–251.
9. Pérez-Yarza EG, Castro-Rodriguez JA, Villa Asensi JR, Garde Garde J, Hidalgo Bermejo FJ. Validation of a Spanish version of the childhood asthma control test (Sc-ACT) for use in Spain. *An Pediatr (Barc).* 2015;**83**:94-103.
10. Nguyen JM, Holbrook JT, Wei CY, Gerald LB, Teague WG, Wise RA; American Lung Association Asthma Clinical Research Centers. Validation and psychometric properties of the Asthma Control Questionnaire among children. *J Allergy Clin Immunol.* 2014;**133**:91-7.
11. Chinellato I, Piazza M, Sandri M, et al. Evaluation of association between exercise-induced bronchoconstriction and childhood asthma control test questionnaire scores in children. *Pediatr Pulmonol.* 2012;**47**:226-32.
12. Leung TF, Ko FW, Wong GW, et al. Predicting changes in clinical status of young asthmatics: clinical scores or objective parameters? *Pediatr Pulmonol.* 2009;**44**:442-9.
13. Wun YT, Chan MS, Wong NM, Kong AY, Lam TP. A curvilinear nomogram of peak expiratory flow rate for the young. *J Asthma.* 2013;**50**:39-44
14. Simoni M, Lombardi E, Berti G, et al., and SIDRIA-2 Collaborative Group. Mould/dampness exposure at home is associated with respiratory disorders in Italian children and adolescents. The SIDRIA-2 Study. *Occup Environ Med.* 2005;**62**:616-22.

15. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Resp J.* 2012;**40**:1324–43.
16. Ricci G, Dondi A, Baldi E, Bendandi B, Giannetti A, Masi M. Use of the Italian version of the Pediatric Asthma Quality of Life Questionnaire in the daily practice: results of a prospective study. *BMC Pediatrics.* 2009;**9**:30.
17. Frank E, Harrell Jr. Rms package Available from: <http://cran.r-project.org/web/packages/rms/rms.pdf>.
18. Koolen BB, Pijnenburg MWH, Brackel HJL, et al. Comparing Global Initiative for Asthma (GINA) criteria with the Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT). *Eur Respir J.* 2011;**38**:561–566.
19. Chipps B, Zeiger RS, Murphy K, et al. Longitudinal Validation of the Test for Respiratory and Asthma Control in Kids in Pediatric Practices. *Pediatrics.* 2012;**129**:595-6.
20. Wong GWK, Kwon N, Hong JG, Hsu J-Y, Gunasekera KD. Pediatric asthma control in Asia: Phase 2 of the Asthma Insights and Reality in Asia-Pacific (AIRIAP 2) survey. *Allergy.* 2013;**68**:524–530.
21. Bloomberg GR, Banister C, Sterkel R, et al. Socioeconomic, family, and pediatric practice factors that affect level of asthma control. *Pediatrics.* 2009;**123**:829-835.
22. Quittner A, Modi A, Cruz I. Systematic review of health-related quality of life measures for children with respiratory conditions. *Paediatr Respir Rev* 2008;**9**:220-32.
23. Mussaffi H, Omer R, Prais D, Computerised pediatric asthma quality of life questionnaires in routine care. *Arch Dis Child.* 2007;**92**:678-82.
24. Tiggeleman D, Van de Ven MO, Van Schayck OC, Engels RC. Longitudinal associations between asthma control, medication adherence, and quality of life among adolescents: result from a cross-lagged analysis. *Qual Life Res.* 2015; DOI 10.1007/s11136-015-0945-3.

25. Okelo SO, Wu AW, Krishnan JA, et al. Emotional Quality of life and outcomes in adolescents with asthma. *J Pediatr*. 2004;**145**:523-9.
26. Guyatt GH, Juniper EF, Griffith LE, Feeny DH, Ferrie PJ. Children and Adult Perceptions of Childhood Asthma. *Pediatrics*. 1997;**99**:165–168.
27. Reichenberg K, Broberg AG. Quality of life in childhood asthma: use of the Paediatric Asthma Quality of Life Questionnaire in a Swedish sample of children 7 to 9 years old. *Acta Paediatr*. 2000; **89**:989-95.
28. Juniper EF. How important is quality of life in pediatric asthma? *Pediatric Pulmonology*. 1997; **S15**:17-21.
29. Everhart RS, Fiese BH. Asthma severity and child quality of life in pediatric asthma: A systematic review. *Patient Education and Counseling*. 2009;**75**:162–168.
30. Deng X, Gebretsadik T, Jin M, et al. Development of a nomogram for identification of asthma among adults in epidemiologic studies. *Ann Allergy Asthma Immunol*. 2010; **105**:203-10

TABLE 1. Demographic characteristics of asthmatic by level of control

|                                       | <i>Well Controlled</i> | <i>Partially Controlled</i> | <i>Uncontrolled Asthma</i> | <i>P Value<sup>#</sup></i> |
|---------------------------------------|------------------------|-----------------------------|----------------------------|----------------------------|
|                                       | <i>WC</i>              | <i>PC</i>                   | <i>UA</i>                  |                            |
| <b><i>Demographic</i></b>             |                        |                             |                            |                            |
| N                                     | 55 (38)                | 37 (26)                     | 52 (36)                    |                            |
| Asthma Severity, n (%)                |                        |                             |                            | <b>&lt;0.0001</b>          |
| Intermittent                          | 42 (76)                | 14 (38)                     | 11 (22)                    |                            |
| Persistent Mild                       | 11 (20)                | 13 (35)                     | 20 (38)                    |                            |
| Persistent Moderate/Severe            | 2 (4)                  | 10 (27)                     | 21 (40)                    |                            |
| Female, n (%)                         | 21(38)                 | 18(49)                      | 18 (35)                    | 0.33                       |
| BMI, mean (SD), kg/m <sup>2</sup>     | 19.34 (4.27)           | 19.16 (4.34)                | 18.42 (4.22)               | 0.51                       |
| Age, mean (SD)                        | 7.98 (1.65)            | 8.28 (1.65)                 | 8.09 (2.09)                | 0.75                       |
| <b><i>Host factors</i></b>            |                        |                             |                            |                            |
| Prematurity (< 37 weeks of gestation) | 6 (11)                 | 5 (14)                      | 5 (10)                     | 0.84                       |
| Breast feeding $\geq 3$ months**      | 29 (54)                | 25 (68)                     | 39 (76)                    | <b>0.05</b>                |

|                                |         |         |         |      |
|--------------------------------|---------|---------|---------|------|
| Parental education: >8 years** | 50 (94) | 30 (81) | 44 (85) | 0.12 |
|--------------------------------|---------|---------|---------|------|

---

***Environmental factors***

|                         |         |         |         |      |
|-------------------------|---------|---------|---------|------|
| Exposure of ETS (yes)** | 23 (43) | 14 (38) | 17 (33) | 0.57 |
|-------------------------|---------|---------|---------|------|

|                             |         |        |         |      |
|-----------------------------|---------|--------|---------|------|
| Exposure to traffic (yes)** | 21 (40) | 9 (24) | 19 (37) | 0.34 |
|-----------------------------|---------|--------|---------|------|

|                               |        |        |         |      |
|-------------------------------|--------|--------|---------|------|
| Current mold exposure (yes)** | 7 (13) | 6 (16) | 11 (22) | 0.53 |
|-------------------------------|--------|--------|---------|------|

---

***Spirometric indices***

|                            |               |                |               |      |
|----------------------------|---------------|----------------|---------------|------|
| FVC % predicted, mean (SD) | 99.54 (10.39) | 104.36 (24.05) | 96.59 (16.67) | 0.12 |
|----------------------------|---------------|----------------|---------------|------|

|                                         |               |               |               |              |
|-----------------------------------------|---------------|---------------|---------------|--------------|
| FEV <sub>1</sub> % predicted, mean (SD) | 99.46 (10.41) | 99.15 (22.36) | 89.63 (17.89) | <b>0.005</b> |
|-----------------------------------------|---------------|---------------|---------------|--------------|

|                                              |              |              |               |                   |
|----------------------------------------------|--------------|--------------|---------------|-------------------|
| FEV <sub>1</sub> /FVC % predicted, mean (SD) | 99.43 (6.59) | 94.84 (8.13) | 92.13 (10.53) | <b>&lt;0.0001</b> |
|----------------------------------------------|--------------|--------------|---------------|-------------------|

|                                             |               |               |               |                  |
|---------------------------------------------|---------------|---------------|---------------|------------------|
| FEF <sub>25-75</sub> % predicted, mean (SD) | 93.93 (20.17) | 91.93 (45.69) | 72.04 (20.94) | <b>&lt;0.001</b> |
|---------------------------------------------|---------------|---------------|---------------|------------------|

---

***Clinical history***

|                                         |             |             |             |                   |
|-----------------------------------------|-------------|-------------|-------------|-------------------|
| Exacerbations last 12 months, mean (SD) | 0.38 (0.82) | 2.06 (2.23) | 4.45 (4.02) | <b>&lt;0.0001</b> |
|-----------------------------------------|-------------|-------------|-------------|-------------------|

---

Data are presented as n (%) or mean (SD); ETS: Environmental Tobacco Exposure; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC : Forced vital capacity; FEF<sub>25-75</sub>: Forced expiratory flow 25–75%; \*Spirometric indices are expressed as percent predict according to GLI2012 equations. \*\*≤ 3 missing values.

#The p-values are from Chi-square test or ANOVA test.

TABLE 2. Generalized linear model for PAQLQ

|         | $\beta$ | SE   | CI95%                | P-value      |
|---------|---------|------|----------------------|--------------|
| C-ACT 2 | 0.05    | 0.02 | <b>[0.023-0.084]</b> | <b>0.001</b> |
| C-ACT 3 | 0.03    | 0.02 | <b>[0.001-0.069]</b> | <b>0.05</b>  |
| C-ACT 6 | 0.04    | 0.01 | <b>[0.014-0.071]</b> | <b>0.01</b>  |
| C-ACT 7 | 0.03    | 0.02 | [-0.007-0.071]       | 0.12         |

Generalized linear model for prediction of PAQLQ, assuming a Gamma family with log link. The model is been obtained through a stepwise procedure starting from a full model with all C-ACT item.  $\beta$ : estimates of the GLM model; SE standard errors of  $\beta$  estimates; CI95%: Confidence Interval at 95% .

### Figure Legends

Figure 1. Distribution of C-ACT by level of control (where: WC: Well Controlled; PC: Partially Controlled; UA: Uncontrolled). Boxes represent the first and the third quartile, the central line is the median, the whiskers indicate the variability outside the first and third quartile, while the dots are the outliers. p-value is obtained by an ANOVA test.

Figure 2. Spearman correlation among C-ACT and PAQLQ (total score and domains). Where PAQLQ: PAQLQ total score, PAQLQ AL: PAQLQ Activity Limitations; PAQLQ S: PAQLQ Symptoms; PAQLQ EF: PAQLQ Emotional Functions; Significant correlations between C-ACT and PAQLQ (total score and domains) were found. The main diagonal reports the variable names, the upper panel reports the color of correlations in square (darker square indicates higher correlation in absolute value), and the lower panel portrays the estimated coefficients. The square color represents the direction of correlation (red=negative correlation, blue=positive correlation).

Figure 3. Nomogram for predicting PAQLQ using four C-ACT item. The predicted values are the result of a GLM model. To obtain the predicted value of QoL the following steps are required: 1) each value of selected C-ACT items has to be reported on the *Points* line (0-100, each bar corresponds to 2.5 units) on the top of the figure; 2) the four obtained scores have to be summed each other; 3) the obtained sum has to be reported on the *Total Points* line (0-400, each bar corresponds to 10 units); 4) the *PAQLQ Predicted Value* will be obtained by tracing a perpendicular segment from the *Total Points* line to the *PAQLQ Predicted Value* line.

Figures S1: Comparing between predicted PAQLQ score and observed PAQLQ score. Colors identify the units classification, so in gray there are the correctly classified while in dark the units misclassified. The dotted lines sign the cutoff ( $\geq 5.3$ ) for observed and predicted PAQLQ score. The classification rate is 70%.

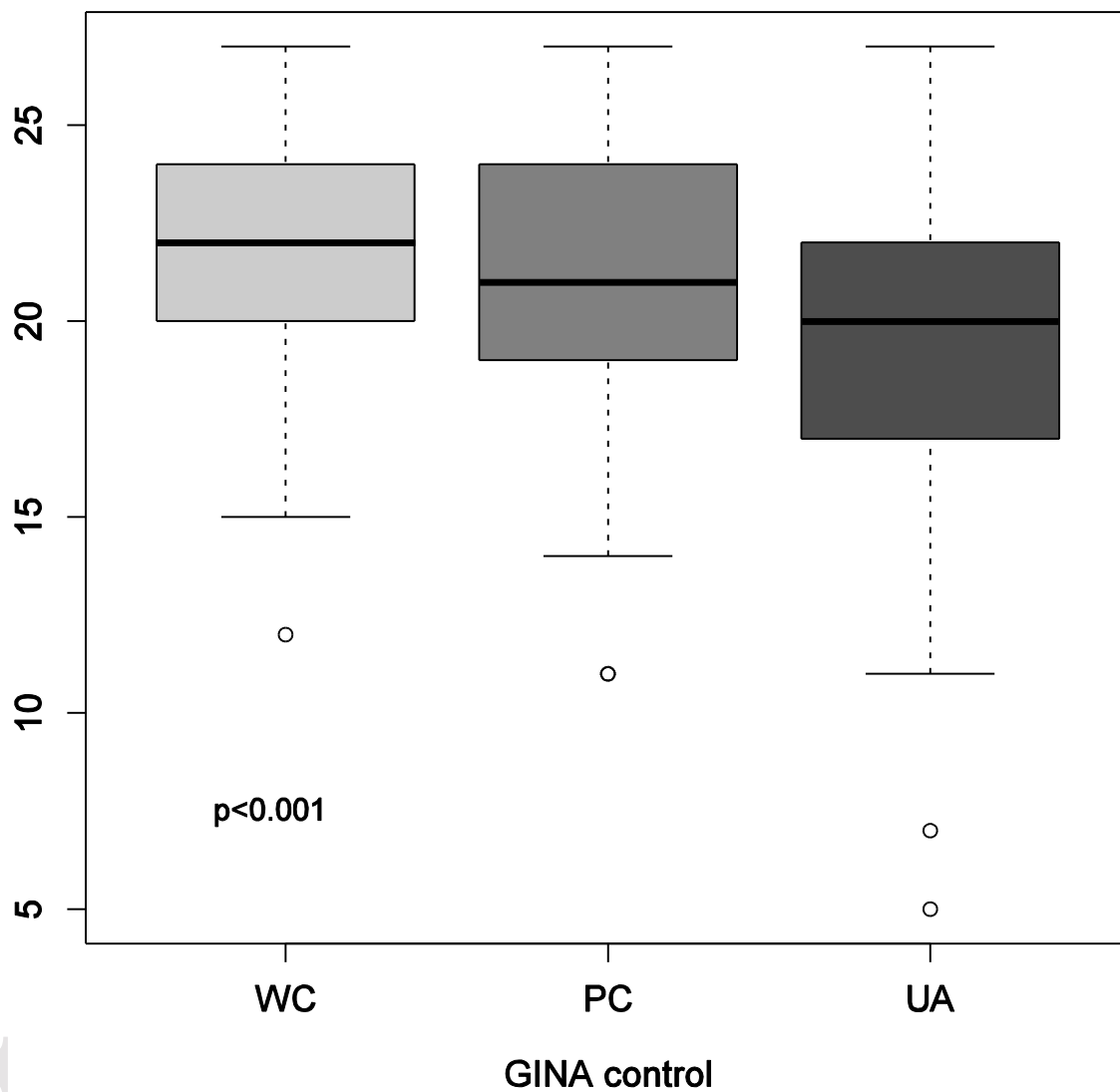


Figure 1. Distribution of C-ACT by level of control (where: WC: Well Controlled; PC: Partially Controlled; UA: Uncontrolled); p-value is obtained by an ANOVA test.

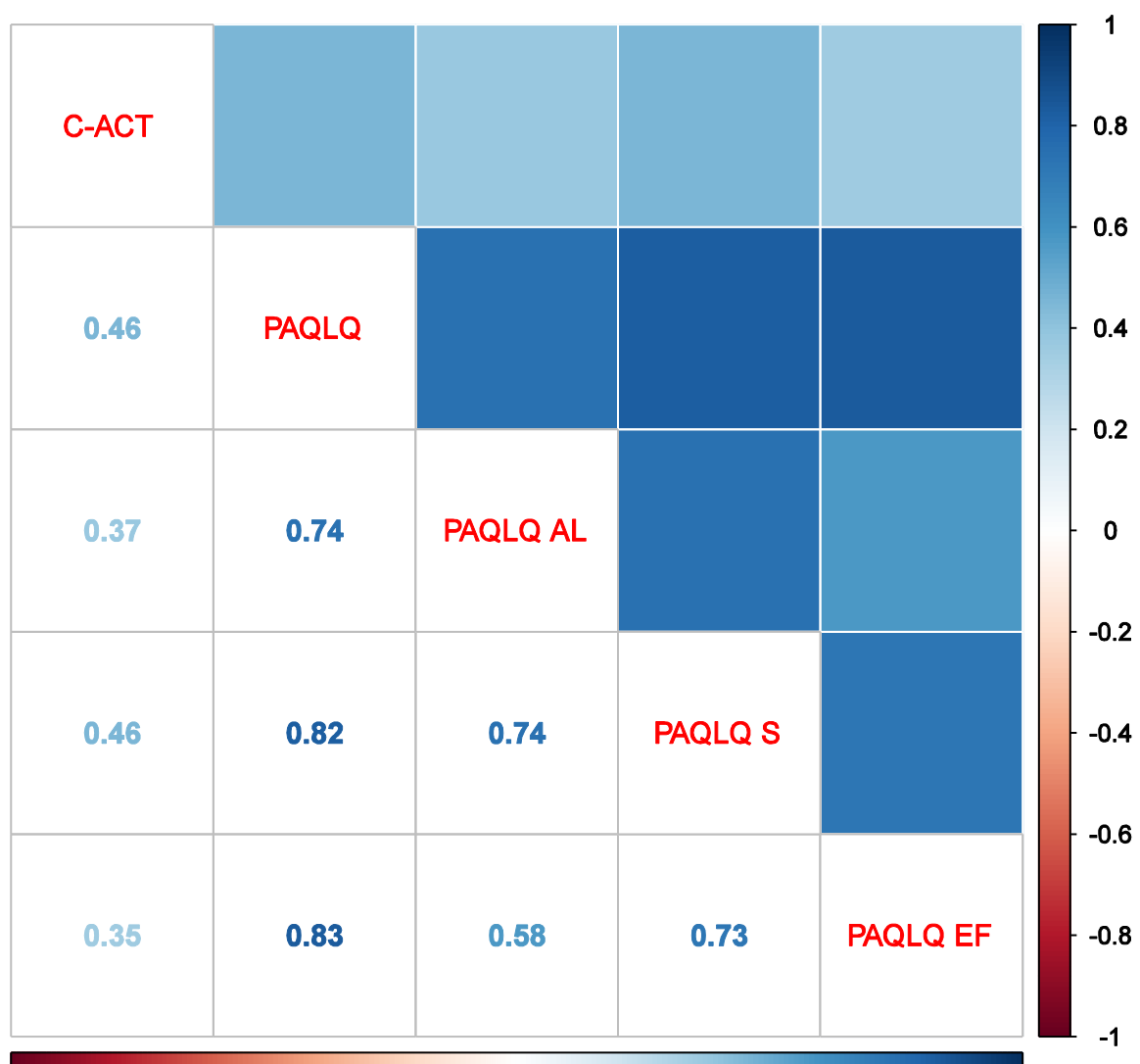


Figure 2. Spearman correlation among C-ACT and PAQLQ (total score and domains). Where PAQLQ: PAQLQ total score, PAQLQ Activity Limitations (AL); PAQLQ Symptoms (S); PAQLQ Emotional Functions (EF); significant correlations between C-ACT and PAQLQ (total score and domains) were found. The main diagonal reports the variable names, the upper panel reports the color of correlations in square (darker square indicates higher correlation in absolute value), and the lower panel portrays the estimated coefficients. The square color represents the direction of correlation (red=negative correlation, blue=positive correlation).

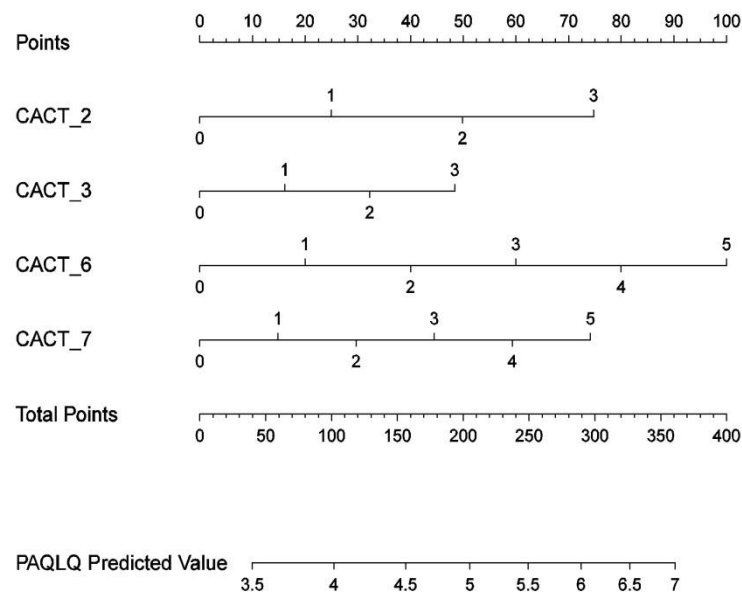
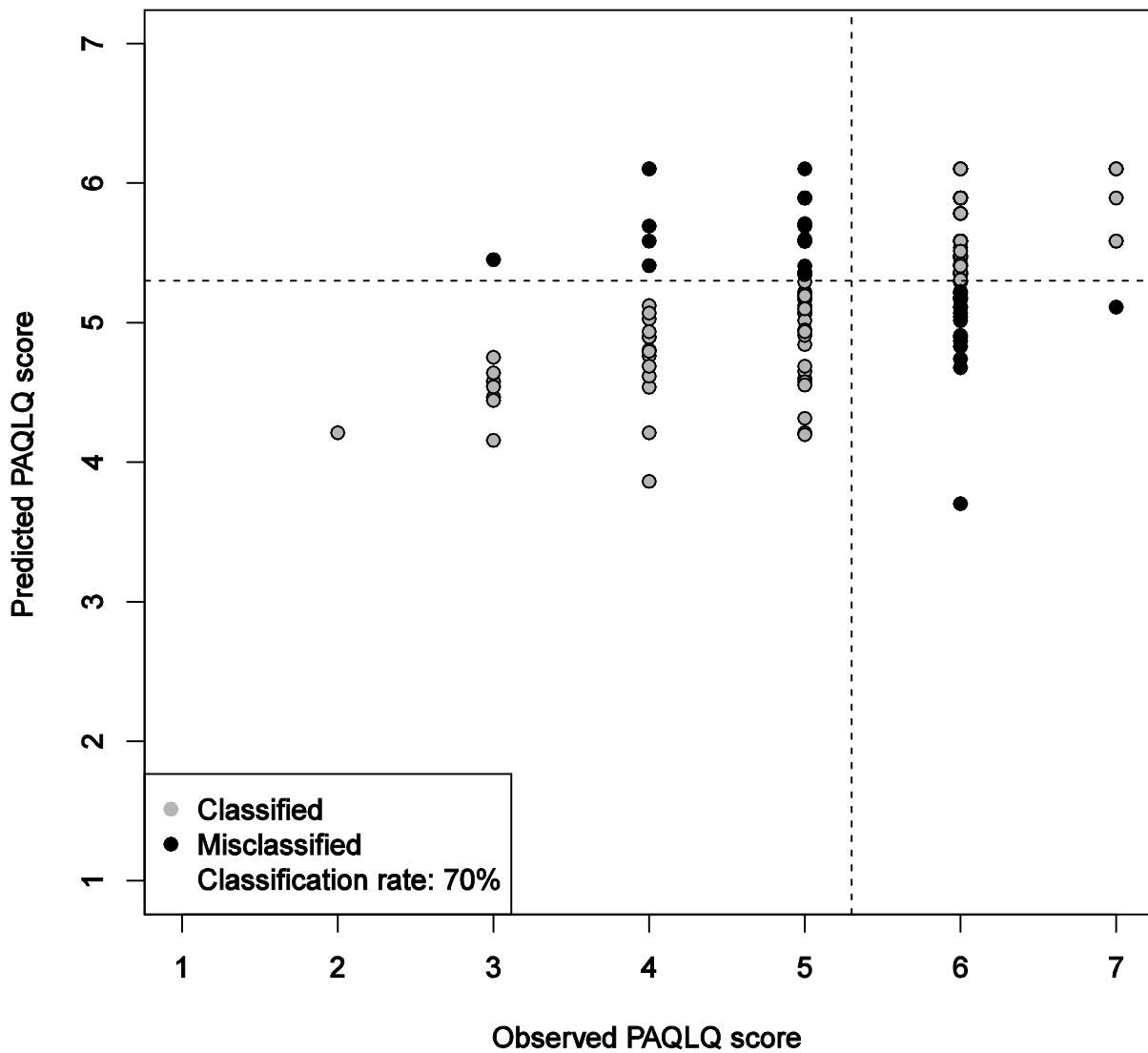


Figure 3. Nomogram for predicting PAQLQ using four C-ACT item. The predicted values are the result of a GLM model. To obtain the predicted value of QoL the following steps are required: 1) each value of selected C-ACT items has to be reported on the *Points* line (0-100, each bar corresponds to 2.5 units) on the top of the figure; 2) the four obtained scores have to be summed each other; 3) the obtained sum has to be reported on the *Total Points* line (0-400, each bar corresponds to 10 units); 4) the *PAQLQ Predicted Value* will be obtained by tracing a perpendicular segment from the *Total Points* line to the *PAQLQ Predicted Value* line.



Figures S1: Comparing between predicted PAQLQ score and observed PAQLQ score. Colors identify the units classification, so in gray there are the correctly classified while in dark the units misclassified. The dotted lines sign the cutoff ( $\geq 5.3$ ) for observed and predicted PAQLQ score. The classification rate is 70%.

TABLE S1. All possible combination of four C-ACT items for predicting PAQLQ

| C-ACT | C-ACT 2 | C-ACT 3 | C-ACT 6 | C-ACT 7 | Total Points | PAQLQ<br>Predicted Value |
|-------|---------|---------|---------|---------|--------------|--------------------------|
| 0     | 0       | 0       | 0       | 0       | <40          | ≤3.5                     |
| 1     | 25      | 16      | 20      | 15      | 41-102       | 3.5-4                    |
| 2     | 50      | 32      | 40      | 30      | 103-156      | 4-4.5                    |
| 3     | 75      | 48      | 60      | 44      | 157-205      | 4.5-5                    |
| 4     |         |         | 80      | 59      | 206-249      | 5-5.5                    |
| 5     |         |         | 100     | 74      | 250-289      | 5.5-6                    |
|       |         |         |         |         | >289         | >6                       |

For each value of C-ACT has been assigned a number between 0 and 100. The sum of the scores, for each profile considered, gives a total score (Total Points) which corresponds to a class of PAQLQ predicted. For example if we want to know the QoL of a children with the following profile:

C-ACT 2 = 2

C-ACT 3 = 1

C-ACT 6 = 3

C-ACT 7 = 2

Total Points= 50+16+60+30=156 so the Predicted PAQLQ will be between 4 and 4.5  
(Intermediate Quality of life)

