Aus der Kinderchirurgische Klinik und Poliklinik im Dr. von Haunerschen Kinderspital

der Universität München

Direktor: Herr Prof. Dr. Oliver Muensterer

Sarcopenia as an outcome marker in children with solid organ malignancies

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von

Annika Ritz

aus

Heidelberg

Jahr

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Mit Genehmigung der Medizinischen Fakultät
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DECLARATION

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Sarcopenia as an outcome marker in children with solid organ malignancies

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Indianapolis, IN, USA 13. April 2023 Annika Ritz

Ort, Datum Unterschrift Doktorandin bzw. Doktorand

DEDICATION

To my parents

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LIST OF ABBREVIATIONS

AFP	alpha-fetoprotein
BIA	bio-electric impedance analysis
BMI	body mass index
CHIC	Children's Hepatic Tumors International Collaboration
CI	confidence interval
COG	Children's Oncology Group
CT	computed tomography
CTx	chemotherapy
DXA	dual-energy x-ray absorptiometry
GPOH	German Society for Paediatric Oncology and Haematology
HB	hepatoblastoma
ICU	intensive care unit
INGRSS	International Neuroblastoma Risk Group Staging System
INPC	the International Neuroblastoma Pathology Classification
INRG	International Neuroblastoma Risk Group
INSS	International Neuroblastoma Staging System
JPLT	Japanese Study Group for Pediatric Liver Tumors
MKI	mitosis-karyorrhexis index
MRI	magnetic resonance imaging
NB	neuroblastoma
PRETEXT	Pretreatment extent of disease
SIOPEL	International Childhood Liver Tumours Strategy Group
tPMA	total psoas muscle area
VPEFR	"V", involvement of vena cava or all three hepatic veins, or both; "P", involvement of portal bifurcation or both right and left portal veins, or both; "E", extrahepatic contiguous tumor extension; "F", multifocal liver tumor; "R", tumor rupture at diagnosis
WHO	World Health Organization

LIST OF FIGURES

LIST OF PUBLICATIONS

The results of this study were published as an abstract and presented at the following Congresses:

1. **Ritz A,** Kappler R, Hubertus J, von Schweinitz D, Berger M, Lurz E
   Sarcopenia as a Nutritional Biomarker in Children with Hepatoblastoma
   50th Congress of the International Society of Paediatric Oncology (SIOP), 2018
   Kyoto, Japan

2. **Ritz A**, Kappler R, Ng V L, Jüni P, Hubertus J, von Schweinitz D, Berger M, Lurz E
   Sarcopenia as an Independent Outcome Marker in Children with Hepatoblastoma
   34. Jahrestagung der Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (GPGE) E.V., 2019
   Munich, Germany

3. **Ritz A**, Kappler R, Ng V L, Jüni P, Hubertus J, von Schweinitz D, Berger M, Lurz E
   Sarcopenia as an Independent Outcome Marker in Children with Hepatoblastoma
   52nd European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Annual Meeting, 2019
   Glasgow, Scotland

4. **Ritz A,** Froeba-Pohl A, Kolorz J, Hubertus J, Ley-Zaporozhan J, Häberle B, Schmid I, Kappler R, Berger M, Lurz E
   Sarkopenie als objektiver Biomarker bei Kindern mit Neuroblastoma
   36. Jahrestagung der Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (GPGE) E.V., 2021
   Basel, Switzerland

The results of this study were published in the following international Journals as **original work**:

1. **Ritz, A**, Kolorz, J, Hubertus, J, et al. Sarcopenia is a prognostic outcome marker in children with high-risk hepatoblastoma. *Pediatr Blood Cancer*. 2021; 68:e28862. https://doi.org/10.1002/pbc.28862

2. **Ritz A**, Froeba-Pohl A, Kolorz J, et al. Total Psoas Muscle Area as a Marker for Sarcopenia Is Related to Outcome in Children With Neuroblastoma. *Front Surg*. 2021;8:718184. Published 2021 Aug 19. doi:10.3389/fsurg.2021.718184

1 MY CONTRIBUTION TO THE PUBLICATIONS

1.1 CONTRIBUTION TO PAPER I: SARCOPENIA IS A PROGNOSTIC OUTCOME MARKER IN CHILDREN WITH HIGH-RISK HEPATOBLASTOMA

My contribution to this paper includes performing all measurements of the total psoas muscle area (tPMA) on heights L3-4 and L4-5, as well as all postoperative follow-up measurements of the tPMA. I compiled preoperative and postoperative information through the hospital's data system (e.g., weight, height, chemotherapy regimen, past medical history, time in hospital after surgery, time in intensive care unit (ICU) after surgery, postoperative sepsis, etc.). With tPMA and anthropometrics, I generated z-scores through various z-score calculators and growth charts. I completed all statistical analyses and wrote the first draft of the paper, thereafter, revising the paper with all authors. I am the sole first author if this paper.

1.2 CONTRIBUTION TO PAPER II: TOTAL PSOAS MUSCLE AREA AS A MARKER FOR SARCOPENIA IS RELATED TO OUTCOME IN CHILDREN WITH NEUROBLASTOMA

Similar to paper I, my contributions to this paper include performing all measurements of the total psoas muscle area (tPMA) on heights L3-4 and L4-5, as well as all postoperative follow-up measurements of the tPMA, compiling preoperative and postoperative information through the hospital's data system (e.g., time in chemotherapy regimen, past medical history, time in hospital after surgery, time in ICU after surgery, postoperative sepsis, etc.). With tPMA and anthropometrics I generated z-scores through various z-score calculators and growth charts. I completed

all statistical analyses and wrote the first draft of the paper, thereafter, revising the paper with all authors.

Dr. Pohl shared the first authorship of this paper with me. She compiled preoperative and postoperative information (e.g., weight, height, histological status, INSS status, NMYC amplification status, tumor localization, relapse, survival, etc.), helped interpret data, critically reviewed the manuscript, and revised the paper.

2 INTRODUCTION

2.1 DEFINITIONS AND PATHOPHYSIOLOGY OF SARCOPENIA

Sarcopenia is a syndrome defined in 2016 by the European Society for Clinical Nutrition and Metabolism (ESPEN) as "the progressive and generalized loss of skeletal muscle mass, strength and function (performance) with a consequent risk of adverse outcomes."[1] The etiology of sarcopenia is divided into primary and secondary causes. Frequently, sarcopenia is associated with the geriatric field, where processes of aging cause a primary breakdown in muscle. Secondary causes of sarcopenia include low physical activity or immobility (disuse), disease-related mechanisms (e.g., neurodegenerative disease, cancer, etc.), medication, endocrine processes, and malnutrition.[1]

2.2 CURRENT NUTRITIONAL ASSESSMENT TECHNIQUES

Traditionally, the nutritional status of children has been predicted by using anthropometric tests such as the body weight, weight-for-age z-scores, height-for-age z-scores, weight-for-height z-scores, body mass index (BMI kg/m2), the mid-arm circumference, the triceps skinfold thickness, or the head circumference.[2,3]

The World Health Organization (WHO) defines:[4]

- underweight as a weight-for-age z-score under -2
- stunting as a height-for-age z-score under -2
- wasted as a weight-for-height z-score under -2

While these methods give doctors a good general overview of health status, the ability to correctly measure these markers depends on the cooperation of the child, and the

resulting measurements may differ according to the respective investigator [5,6]. In pediatric cancer patients, large tumor masses, the state of hydration during chemotherapy, and edema due to corticosteroid treatment can influence the weight of the patient, masking loss of fat and skeletal muscle.[3] Thus, anthropometric tests may not be an appropriate tool for children with cancer.

Nutritional risk assessment scores are also used to assess factors like anthropometry, biochemical changes, dietary intake, and clinical assessment.[7-9, 10] To date, one assessment tool has not been found to be superior according to its predictive accuracy and no standard clinical guidelines to assess and monitor for nutritional status in children with cancer exists.[11]

2.3 Assessing for Sarcopenia and Current Research

Multiple validated techniques exist to measure muscle mass and assess for sarcopenia, including dual-energy x-ray absorptiometry (DXA), bio-electric impedance analysis (BIA), cross-sectional computed tomography (CT) scanning, and cross-sectional magnetic resonance imaging (MRI).[1-3] One widely used technique measures the total psoas muscle area (tPMA) using CT or MRI imaging by identifying the left and right psoas muscle on a single slice image between lumbar heights L3 and L5. [2,12-16] The surface areas are then measured, the results are added, and the tPMA is calculated. In a variety of patient groups, the tPMA has been identified as a prognostic marker to predict outcome.[2,12-19]

Both the prevalence, consequences, and treatment of sarcopenia in the elderly and whether sarcopenia predicts outcome in adults with chronic illnesses have become popular research topics. [20-23]. In contrast, limited research has been published on

sarcopenia in the pediatric population, especially in children with cancer. [24] With the help of recently published gender- and age-specific pediatric tPMA z-scores at heights L3-4 and L4-5, the assessment of sarcopenia has become more standardized. More research is needed to determine the impact of sarcopenia in children with malignancies.[25]

2.4 HEPATOBLASTOMA AND NEUROBLASTOMA

2.4.1 *Hepatoblastoma*

In western countries, hepatoblastoma (HB) is the most common primary liver tumor and the third most common abdominal tumor in children.[26] Although HB only accounts for 1% of childhood malignancies, in the last 30 years its incidence in the USA, Europe, and Japan has been steadily increasing. HB is most frequently diagnosed between 0 and 5 years of age and makes up the largest portion of diagnosed liver malignancies in this age range.[26,27]

At diagnosis 10-20% of patients present with metastases, most frequently to the lung.[28] About 80-90% of patients with HB present with high levels of serum alpha-fetoprotein (AFP) (>1000 ng/ml).[26,29,30] Extremely low AFP levels (<100 ng/mL) and extremely high AFP levels (>$1x10^6$ ng/ml) are associated with a more aggressive tumor and a poor outcome.[31-33] Restrictions of this marker include its potential elevation in patients with benign liver tumors and its physiological elevation in infants.[26]

When working up this tumor, an abdominal ultrasound is initially performed to determine the location of the tumor and to show possible hepatic and portal vein invasion. Later, CT or MRI imaging is used to show morphologic details, differentiate

between liver tumors, check for pulmonary metastasis, and asses the lymph node status.[26,34]

2.4.1.1 Staging and Risk Stratification

Four different trial groups, the International Childhood Liver Tumours Strategy Group (SIOPEL), Children's Oncology Group (COG), German Society for Paediatric Oncology and Haematology (GPOH), and Japanese Study Group for Pediatric Liver Tumors (JPLT), have published prospective randomized studies on HBs in the last two decades. This research has led to the discovery of various risk factors linked to HBs and the development of numerous risk classification systems. In 1990, SIOPEL introduced the PRETEXT (Pretreatment extension of disease) staging system, which assesses risk based on pretreatment imagining.[35] The PRETEXT groups use Couinaud's system of segmentation of the liver to express the intrahepatic extent of primary tumor(s) growth. See Figure 1. Studies demonstrate that the PRETEXT system shows predictive value for survival, with PRETEXT I having the best overall 5-year survival and PRETEXT IV having the worst.[36,37] Besides PRETEXT number, the PRETEXT staging system described the presence of additional criteria, with each criteria given a specific letter. In 2005 the criteria, were revised to better define PRETEXT groups and further categories were added.[38]

PRETEXT number	Definition
I	1 section is involved and 3 adjoining sections are free
II	1 or 2 sections are involved, 2 adjoining sections are free
III	2 or 3 sections are invovled, No 2 adjoining sections are free
IV	All 4 sections are involved

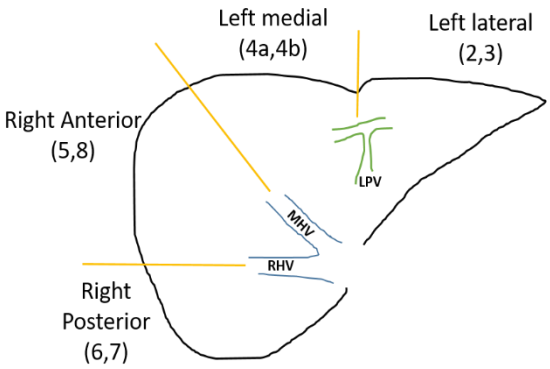

Figure 1. PRETEXT Stages
(left) Table shows definitions of PRETEXT categories. (right) Figure shows four sections of the liver with numerals labeling Couinaud's segments 2-8 included in each section. Abbreviations: RHV: Right hepatic vein; MHV: Middle hepatic vein; LPV: Left portal vein

Due to the difficulty comparing various existing staging systems for HB, the Children's Hepatic Tumors International Collaboration (CHIC), an international tumor database, was formed as an effort by the four major trial groups to develop a unified, global strategy to assess risk stratification and clarify risk factors. First published in 2016, Meyers et al. evaluate diagnostic factors of 1605 patients treated in eight multicenter trails over 25 years and define four distinct risk groups (very low, low-, intermediate-, and high-risk) based on 5-year event-free survival and clinical applicability. Factors influencing risk status include PRETEXT group, metastases, age at diagnosis, AFP level, and the presence of revised PRETEXT annotation factors (VPEFR+ when one of the following is present: "V", involvement of vena cava or all three hepatic veins, or both; "P", involvement of portal bifurcation or both right and left portal veins, or both; "E", extrahepatic contiguous tumor extension; "F", multifocal liver tumor; "R", tumor rupture at diagnosis).[35,38]

2.4.2 *Neuroblastoma*

Arising from the neural crest during fetal or postnatal development, neuroblastoma (NB) is the most common solid extracranial malignancy of childhood and the most common malignant tumor in infants. NB accounts for an unproportionable 15% of pediatric cancer deaths, although it only causes 8% of malignancies in children under 15 years of age.[39] "Neuroblastoma" is an umbrella term, referring to an array of tumors including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas. This may account for its epidemiological, histological, molecular, and positional heterogeneity.[40]

NB can occur anywhere in the sympathetic nervous system, with the majority (40%) of tumors located in the adrenal gland. The abdominal (25%), thoracic (15%), cervical (5%), and pelvic (5%) sympathetic ganglia are also a common site.[41] About 60% of patients have metastatic disease at diagnosis, most often to the bone marrow or cortical bone.[42]

Similar to HB, sonography is a noninvasive way to initially find large NB tumors, including in prenatal screenings. CT and MRI images are then used to better determine anatomical tumor location, tumor stage, and surgical treatment options.

2.4.2.1 Histology and Genetics

NBs are classified into four groups by histopathology: neuroblastomas, ganglioneuroblastoma-intermixed, ganglioneuroblastoma-nodular, and ganglioneuroma. Although ganglioneuromas are benign, their large size and tendency to infiltrate can increase surgical risks. According to the International Neuroblastoma Pathology Classification (INPC), ganglioneuroblastoma-intermixed and

ganglioneuroma are always considered favorable, while NB and ganglioneuroblastoma, nodular are classified as unfavorable or favorable tumor subtypes dependent on mitosis-karyorrhexis index (MKI) and age-linked evaluation of neuroblastic differentiation grade (differentiating, poorly differentiated, and undifferentiated).[43-47]

Only 1-2% of NBs are familial, while the majority arise sporadically. About 50% of cases have a chromosomal deletion, most frequently on chromosomes 1p, 11q, and 14q. A deletion of chromosome 1p is associated with an amplification and overexpression of the proto-oncogene MYCN.[40] Both an amplification of MYCN (found in 25% of NB patients) and a deletion of chromosomes 1p and 11q (present in 30% of patients) are associated with poor outcomes.[39]

2.4.2.2 Staging and Risk Stratification

The first internationally recognized classification system for the NB is the International Neuroblastoma Staging System (INSS). Based on the old Evans-Classification, which categorizes NB by clinical and radiological findings, the INSS goes a step further to include surgical and histologic findings.[39,48] Patients with stage 1 localized tumors which are completely resectable have better overall survival than patients diagnosed with stage 3 and stage 4 disseminated metastatic tumors. Patients with stage 4 tumors have the worst survival outcomes.[49,50] While the INSS is prognostic, its implications are limited because non-surgical patients with NB cannot be assessed, lymph node evaluation is necessary, and comparability among patients in the same class may be difficult because same tumors can have different stages depending on resectability.[39,51]

The International Neuroblastoma Risk Group Staging System (INGRSS) was developed to categorize NBs preoperatively by looking for the absence (L1) or presence (L2) of 20 image defining risk factors.[39,51] Stage L1 describes a localized tumor that is confined to one body compartment and does not involve vital structures. Additionally, stage "M" is used to label a metastatic disease, and "MS" labels a metastatic disease confined to the skin, liver and/or bones marrow in children < 18 months.[51] The International Neuroblastoma Risk Group (INRG) classification system uses the INGRSS, age, histologic category, grade of tumor differentiation, MYNC status, 11q aberration status, and tumor cell ploidy to stratify risk. Especially the presence of MYCN amplification is an important factor in stratifying patients into the high pretreatment risk group.[45]

2.5 Goals of the Study

Within the study, two papers were published presenting our results on sarcopenia as an outcome marker in children with HB and in children with NB. In our research, we aimed to determine whether children with HB and NB were sarcopenic prior to tumor surgery. We hypothesized that children with HB or NB had very low tPMA compared to age- and gender matched peers prior to surgery, showing they were sarcopenic. We simultaneously measured traditional anthropometric markers (e.g., height and weight) and postulated that weight, height, and BMI z-scores would be in the normal range. We aimed to determine if the tPMA can be used as a predictor of outcome (e.g., surgical complications, sepsis, time in intensive care unit (ICU), time in hospital after surgery, relapse, and survival) and hypothesized that the tPMA z-score and sarcopenia are better predictors of outcome than traditional anthropometric markers. Lastly, we

remeasured the tPMA after surgery to see if an increase in tPMA correlated with better patient outcome.

3 SUMMARY

In these two retrospective studies, we expanded our understanding of the relationship between sarcopenia and outcome in children with HB and NB. Our results showed that the average pediatric patient with HB and NB is sarcopenic, defined by a tPMA z-score < -2. In contrast, most children in both groups had traditional anthropometric markers (weight, height, BMI) within two standard deviations of the norm, indicating that the use of weight and height to determine low lean muscle mass is inadequate. In both groups, girls had lower tPMA z-scores than males, though they did not have less favorable diseases statuses (e.g., PRETEXT 4 or VPEFR+). Further research is needed to determine why this may be the case and whether girls may be more likely to be sarcopenic before surgery because they are more vulnerable to chemotherapy or tumor processes. In both patient cohorts, no significant relationship was found between sarcopenia and short-term outcome. In children with HB and high-risk disease, children who were sarcopenic prior to surgery had a higher likelihood of relapse. Due to the small sample size and few events, in children with HB, survival could not be accounted for. In children with NB, sarcopenia was a risk factor for lower five-year survival rates. Age at diagnosis, unfavorable tumor histology, and NB2004-HR chemotherapy were also risk factors for reduced 5-year survival.

While the concept of sarcopenia is gaining popularity, few studies exist to apply the concept of sarcopenia to the pediatric cancer population. Within these studies, definitions and methods still vary greatly. Using a recently published pediatric z-score calculator, we determined that preoperatively measured tPMA from readily available cross-sectional imaging is easy to use in children with HB and NB and might

provide prognostic value for postoperative outcome. With this knowledge, more research is needed to further study the influences of factors, such as chemotherapy, on muscle mass and whether we are able to positively influence outcome by increasing muscle mass during the course of the disease.

4 ZUSAMMENFASSUNG

In den beiden vorliegenden retrospektiven Studien haben wir unser Verständnis der Sarkopenie und des Outcomes bei Kindern mit HB und NB vertieft. Die Ergebnisse zeigten, dass der durchschnittliche pädiatrische Patient mit HB und NB sarkopen (definiert durch einen tPMA-z-score < -2) ist. Im Gegensatz dazu wichen in beiden Gruppen bei den meisten dieser Kinder traditionelle anthropometrische Marker (Gewicht, Größe, BMI) weniger als zwei Standardabweichungen von der Norm ab. Dies weist darauf hin, dass die Verwendung von Gewicht und Größe zur Bestimmung einer geringen fettfreien Muskelmasse unzureichend ist. In beiden Gruppen hatten Mädchen niedrigere tPMA z-Scores als Jungs, obwohl sie kein ungünstigeres Krankheitsstadium aufwiesen (z. B. PRETEXT 4 oder VPEFR+). Weitere Untersuchungen sind erforderlich, um festzustellen, warum dies der Fall ist und ob Mädchen vor einer Operation deshalb eher an Sarkopenie leiden, weil sie anfälliger für Chemotherapie oder Tumorprozesse sind. In beiden Patientenkohorten wurde kein signifikanter Zusammenhang zwischen Sarkopenie und dem kurzfristigen Outcome gefunden. Bei Kindern mit HB in der Hochrisikogruppe hatten Patienten, die vor der Operation sarkopen waren, eine höhere Wahrscheinlichkeit eines Rückfalls. Aufgrund der geringen Stichprobengröße und wenigen Ereignissen konnte bei Kindern mit HB das Überleben nicht berücksichtigt werden. Bei Kindern mit NB war Sarkopenie, ebenso wie ein frühes/spätes Erkrankungsalter, eine ungünstige Tumorhistologie und eine NB2004-HR-CTx, ein Risikofaktor für ein reduziertes 5-Jahres-Überleben.

Während die Bedeutung der Sarkopenie für Krankheitsverläufe an Popularität gewinnt, gibt es nur wenige Studien, die dieses Konzept auf Kinder mit onkologischen Erkrankungen anwenden. Innerhalb dieser Studien variieren Definitionen und Methoden noch stark. Mit einem kürzlich veröffentlichten pädiatrischen Z-Score-Rechner konnten wir feststellen, dass die präoperative Verwendung einfach zu handhabender und nicht-invasiver tPMA-Messungen bei Kindern mit HB und NB mehr Einblick in das postoperative Ergebnis geben kann. Basierend auf dieser Erkenntnis sind weitere Untersuchungen erforderlich, um den Einfluss von Faktoren wie Chemotherapie auf die Muskelmasse näher zu untersuchen. Weiterhin sollte analysiert werden, ob das Ergebnis durch eine Zunahme der Muskelmasse im Verlauf der Krankheit positiv beeinflusst werden kann.

5 ABSTRACT

5.1 PAPER I: SARCOPENIA IS A PROGNOSTIC OUTCOME MARKER IN CHILDREN WITH HIGH-RISK HEPATOBLASTOMA

Background: Children with hepatoblastoma (HB) are at risk of sarcopenia due to immobility, chemotherapy, and malnutrition. We hypothesized that children with HB have a low preoperative total psoas muscle area (tPMA), reflecting sarcopenia, which negatively impacts outcome.

Procedure: Retrospective study of children (1-10 years) with hepatoblastoma treated at a large university children's hospital from 2009 to 2018. tPMA was measured as the sum of the right and left psoas muscle area (PMA) at intervertebral disc levels L3-4 and L4-5. *z*-Scores were calculated using age- and gender-specific reference values and were compared to anthropometric measurements, clinical variables, and outcomes. Sarcopenia was defined as a tPMA *z*-score below −2.

Results: Thirty-three children were included. Mean tPMA *z*-score was −2.18 ± 1.08, and 52% were sarcopenic. A poor correlation between tPMA and weight was seen (r = 0.35; confidence interval [CI] 0.01, 0.62; P = .045), and most children had weights within the normal range (mean *z*-score −0.55 ± 1.39). All children categorized as high risk with relapse (n = 5/12) were sarcopenic before surgery. Relapse was significantly higher in the high-risk sarcopenic group compared to the nonsarcopenic group (P = .008). The change in tPMA *z*-score 1-4 months after surgery did not improve in patients with relapse, but did improve in 75% of children without relapse.

Conclusions: The majority of children with HB were sarcopenic prior to surgery. Especially in children with high-risk hepatoblastoma, sarcopenia is an additional risk

factor for relapse. Large multicenter studies are needed to confirm these preliminary results

5.2 Paper II: Total Psoas Muscle Area as a Marker for Sarcopenia Is Related to Outcome in Children With Neuroblastoma

Background: Sarcopenia describes a generalized loss of skeletal muscle mass, strength, or function. Determined by measuring the total psoas muscle area (tPMA) on cross-sectional imaging, sarcopenia is an independent marker for poor post-surgical outcomes in adults and children. Children with cancer are at high risk for sarcopenia due to immobility, chemotherapy, and cachexia. We hypothesize that sarcopenic children with neuroblastoma are at higher risk for poor post-operative outcomes.

Patients and Methods: Retrospective analysis of children with neuroblastoma ages 1–15 years who were treated at our hospital from 2008 to 2016 with follow-up through March 2021. Psoas muscle area (PMA) was measured from cross-sectional images, using computed tomography (CT) and magnetic resonance imaging (MRI) scans at lumbar disc levels L3-4 and L4-5. tPMA is the sum of the left and right PMA. Z-scores were calculated using age- and gender-specific reference values. Sarcopenia was defined as a tPMA z-score below −2. A correlation of tPMA z-scores and sarcopenia with clinical variables and outcome was performed.

Results: One hundred and sixty-four children with workup for neuroblastoma were identified, and 101 children fulfilled inclusion criteria for further analysis, with a mean age of 3.92 years (SD 2.71 years). Mean tPMA z-score at L4-5 was −2.37 (SD 1.02). Correlation of tPMA z-score at L4-5 with weight-for-age z-score was moderate

(r = 0.54; 95% CI, 0.38, 0.66). No association between sarcopenia and short-term outcome was observed. Sarcopenia had a sensitivity of 0.82 (95% CI, 0.62–0.93) and a specificity of 0.48 (95% CI 0.36–0.61) in predicting 5-year survival. In a multiple regression analysis, pre-operative sarcopenia, pre-operative chemotherapy in the NB2004 high-risk group, unfavorable tumor histology, and age at diagnosis were associated with 5-year survival after surgery, with hazard ratios of 4.18 (95% CI 1.01–17.26), 2.46 (95% CI 1.02–5.92), 2.39 (95% CI 1.03–5.54), and 1.01 (95% CI 1.00–1.03), respectively.

Conclusion: In this study, the majority of children had low tPMA z-scores and sarcopenia was a risk factor for decreased 5-year survival in children with neuroblastoma. Therefore, we suggest measuring the tPMA from pre-surgical cross-sectional imaging as a biomarker for additional risk stratification in children with neuroblastoma.

6 PAPER I: SARCOPENIA IS A PROGNOSTIC OUTCOME MARKER IN CHILDREN WITH HIGH-RISK HEPATOBLASTOMA

Original work can be accessed here:

Ritz, A, Kolorz, J, Hubertus, J, et al. Sarcopenia is a prognostic outcome marker in children with high-risk hepatoblastoma. *Pediatr Blood Cancer*. 2021; 68:e28862. https://doi.org/10.1002/pbc.28862

7 PAPER II: TOTAL PSOAS MUSCLE AREA AS A MARKER FOR SARCOPENIA IS RELATED TO OUTCOME IN CHILDREN WITH NEUROBLASTOMA

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Ritz A, Froeba-Pohl A, Kolorz J, et al. Total Psoas Muscle Area as a Marker for Sarcopenia Is Related to Outcome in Children With Neuroblastoma. *Front Surg*. 2021;8:718184. Published 2021 Aug 19. doi:10.3389/fsurg.2021.718184

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