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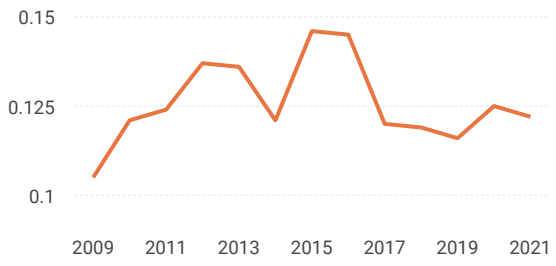

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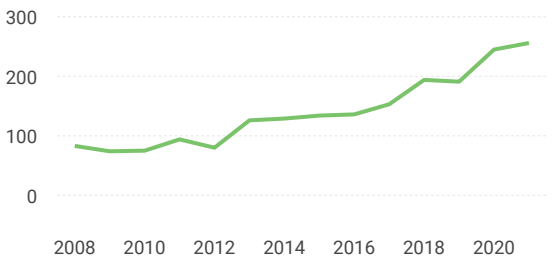

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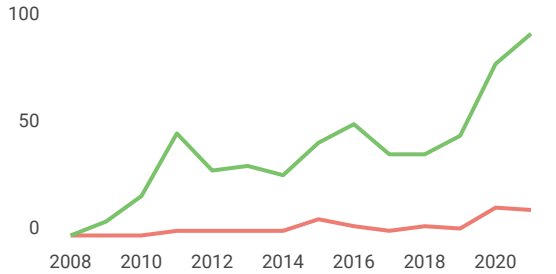

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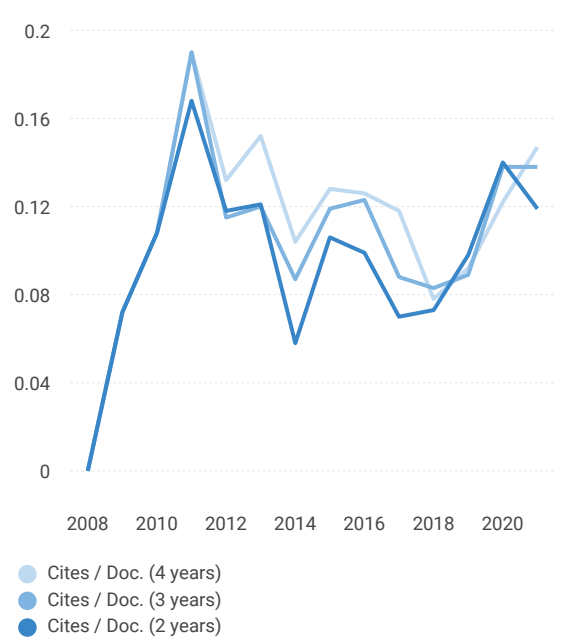

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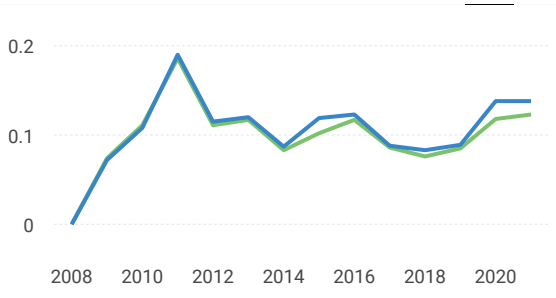

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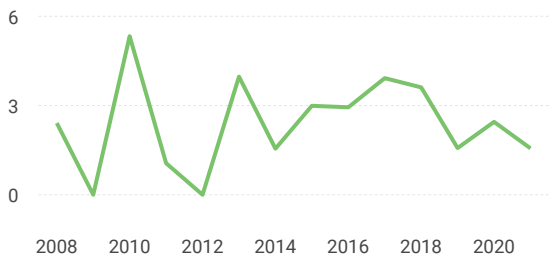

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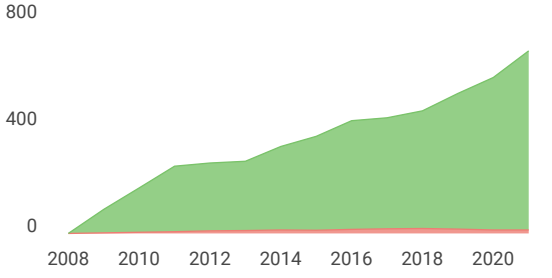

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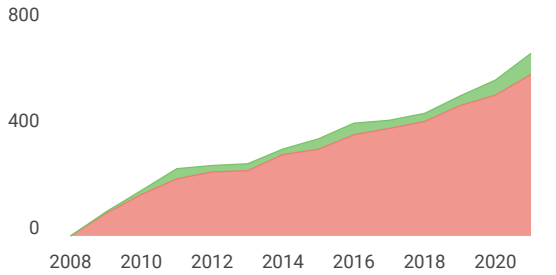

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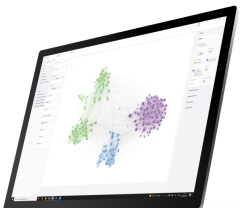

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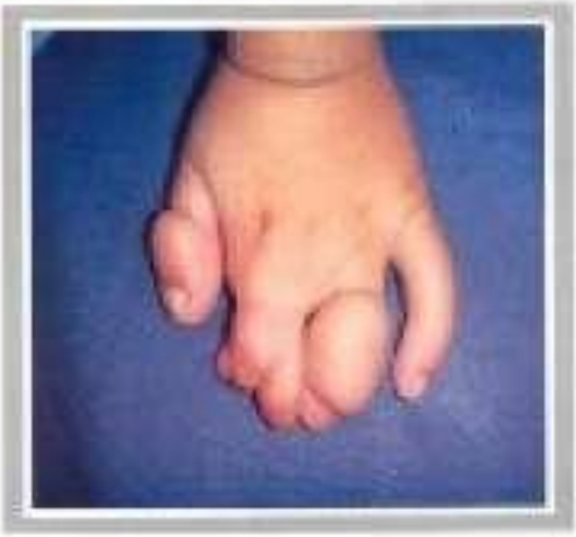

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RAWAL MEDICAL JOURNAL

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Original Article

Total Neuropathy Scale Pediatric Vincristine to detect vincristine induced peripheral neuropathy in children with Acute Lymphoblastic Leukemia

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Department of Child Health, Soetomo General Hospital, Surabaya, Indonesia

Objective: To analyze the Total Neuropathy Scale Pediatric Vincristine (TNS-PV) score as a vincristine induced peripheral neuropathy **(**VIPN) diagnostic tool.

Methodology: This observational analytic study was conducted in Outpatient Pediatric Hematology Oncology Dr. Soetomo Hospital. The inclusion criteria were Acute Lymphoblastic Leukemia (ALL) children aged 4 – 18 years that had undergone chemotherapy treatment, received a cumulative dose of vincristine > 12 mg/m^2, had no muscle weakness and signed informed consent. The TNS-PV instrument were used to assess VIPN and nerve conduction studies (NCS) was used as the gold standard.

Results: A total of 54 children were enrolled, two refused to sign the informed consent. About 60% were male children, 76.9% aged < 10 years old, and 94% were ALL-L1. The TNS-PV had an area under the curve (AUC) of 0.638 (95% CI 0.531-0.834) with cut off value of 3.5. It had a sensitivity 87.9%; specificity 42.1%, positive predictive value 72.5%; negative predictive value (NPV) 66.6% and OR (Odds ratio) 5,273.

Conclusion: TNS-PV score cannot replace NCS as the gold standard, but TNS-PV can be an alternative tool for diagnosing VIPN.

Keywords: Acute lymphoblastic leukemia, total neuropathy scale pediatric vincristine, vincristine induced peripheral neuropathy.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is one of the most common cancers in children. It is the most common type in children, which is about 75%.[1,2] Chemotherapy often results in nerve damage, which is usually caused by drugs, length of therapy, cumulative doses, and substances containing neurotoxics.[3,4] Vincristine induced peripheral neuropathy (VIPN) is a form of peripheral neuropathy that manifest as motor, sensory, and autonomic nerve disorders that occur after vincristine therapy.[2]

The incidence of VIPN is 100% in ALL children undergoing chemotherapy, of which 28% are experience severe symptoms, and cases of VIPN that are not properly treated have negative and disruptive effects and reduce quality of life.[5,6] Severe types of peripheral neuropathy caused by chemotherapy usually improve after chemotherapy protocol is completed, but about 8% persisted mainly due to vincristine.[7,8]

There are several methods of diagnosing peripheral neuropathy in children, some use subjective facial expression scales with Wong Baker FACES, six are objective, such as neurological physical examination, Nerve conduction study (NCS), Electromyography (EMG), Vibration perception threshold (VPT), Tactile perception threshold (TPT) and Current perception threshold (CPT). There are three methods that use subjective and objective judgments, such as the pediatric- modified Total Neuropathy Scale (ped-m TNS), Common Terminology Criteria for Adverse Events (CTCAEv3.0/v4.0) and Total Neuropathy Scale Pediatric Vincristine (TNS-PV).[9]

TNS-PV was a tool used for assessing the peripheral neuropathy identified based on the evidence.[9] TNS-PV review is used as a simple, inexpensive, and non-invasive diagnostic tool for diagnosing VIPN. This study aims to determine the diagnostic value of the TNS-PV in diagnosing VIPN in children with ALL receivingvincristine chemotherapy.

METHODOLOGY

This observational analytical study was conducted at the outpatient Pediatric Hematology-Oncology and Physical Medicine and Rehabilitation Dr. Soetomo General Academic Hospital, from August-October 2019. The study was approved by the Clinical Research Unit of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ref No. 1363/KEPK/VIII/2019).The informed consent was signed by parents or legal guardian of the children.

The subjects were ALL children of age 4 – 18 years old, which had undergone chemotherapy treatment and received a cumulative dose of vincristine > 12 mg/m^2. Patients were excluded when they failed to cooperate during the NCS procedure, had intracranial disorders with manifestations of decreased consciousness, motor, sensory, and autonomic nerve disorders, diabetes

mellitus, thrombocytopenia, or incomplete medical record.

The subjects were interviewed and assessed using TNS-PV questionnaires by a competent pediatric neurologist and the gold standard used for this study was NCS examination (Cadwell Sierra Summit EMG 4 channel, No CDSM05, USA). The NCS examination was carried out by a certified doctor from the department of physical medicine and rehabilitation, and the identification of VIPN was also confirmed by a Pediatric Neurology Consultant.

Items assessed in TNS-PV were subjective symptoms, temperature, vibration, strength, tendon reflexes, autonomic neuropathy (constipation) and laryngeal neuropathy (hoarseness). Those seven items scored 0 – 4 on Likert-type scale. Total scores of TNS-PV considered in range from 0 to 28, the higher scores indicate more severe peripheral neuropathy.

Statistical Analysis: The coded data were analyzed using SPSS version 21. The sensitivity and specificity were calculated using Receptor operating characteristic (ROC curve) analysis to find the cutoff value of the TNS-PV total score for screening the outcome.

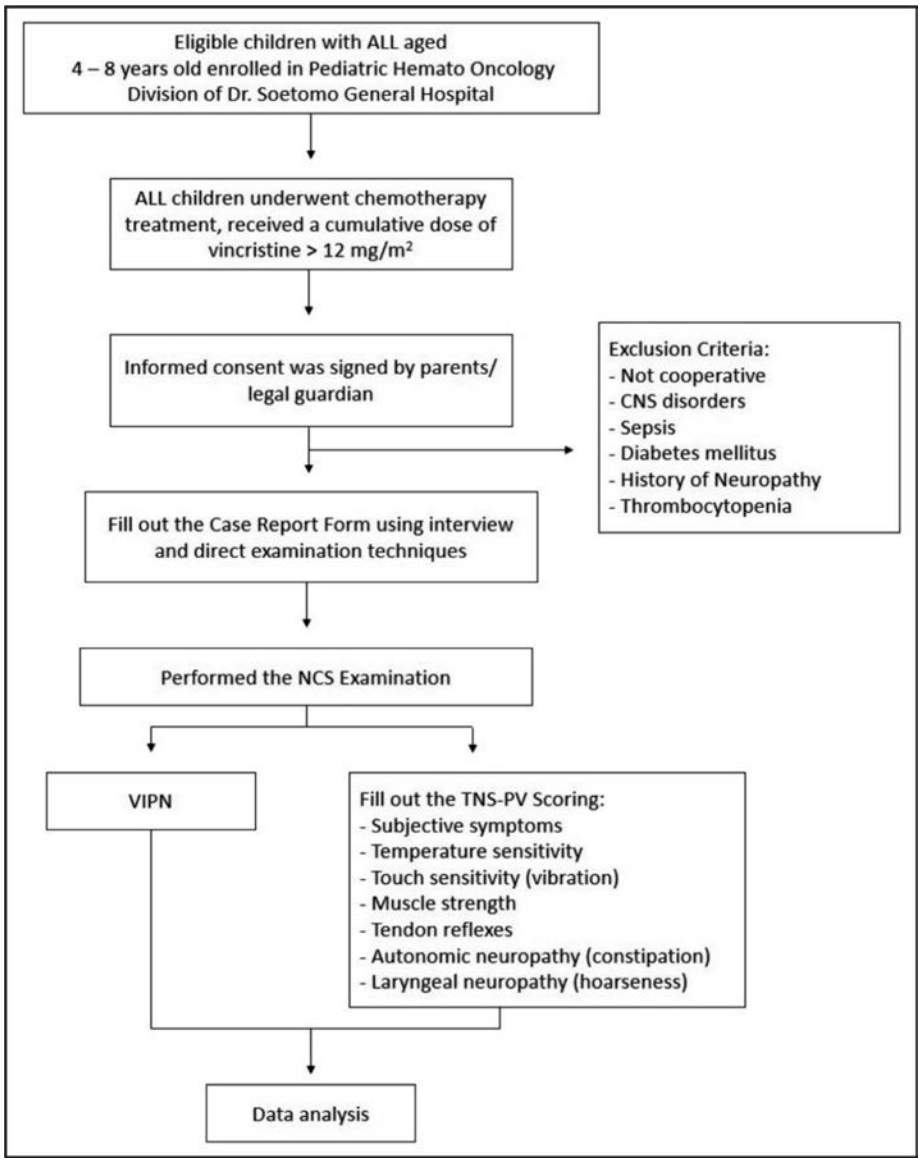

Fig. 1: Research flow chart.

RESULTS

Fifty-four children participated in this study. However, two refused to take part in further examination, therefore a total of 52 subjects participated (Fig. 1). The clinical characteristics of ALL children are presented in Table 1. VIPN that diagnosed with combination test detected in 29 (55.8%) subjects. The TNS-PV has an area under the curve (AUC) of 0.638 (95% CI 0.531 – 0.834) with cutoff value of 3.5 (Fig. 2). Sensitivity of TNS-PV was found to be 78.8% (Table 2).

DISCUSSION

The study showed that male ALL children were more than female. Various studies on ALL children showed that approximately 52.3 – 66.3% ALL patients were male.[10-12] Most children that survive ALL had a mean age of 11. Mean age at diagnosis of ALL was 6 years.[11] Good nutritional status is the largest percentage of ALL children in this study. ALL children were reported to have the healthiest weight status and that 30.6% were underweight, the risk of being overweight was 16.6% and being overweight by 26.7%.[13]

Peripheral neurotoxicity, including sensory and motor skills, accompanied by pain, is almost common when using vincristine for children. Neuropathic symptoms were seen in 82.5% of 40 ALL patients during chemotherapy.[14] Systemic and intrathecal chemotherapy are predisposing factors, and it was reported that 24% children had neuropathy after receiving vincristine.[14] It was stated that sensory peripheral neuropathy occurs at

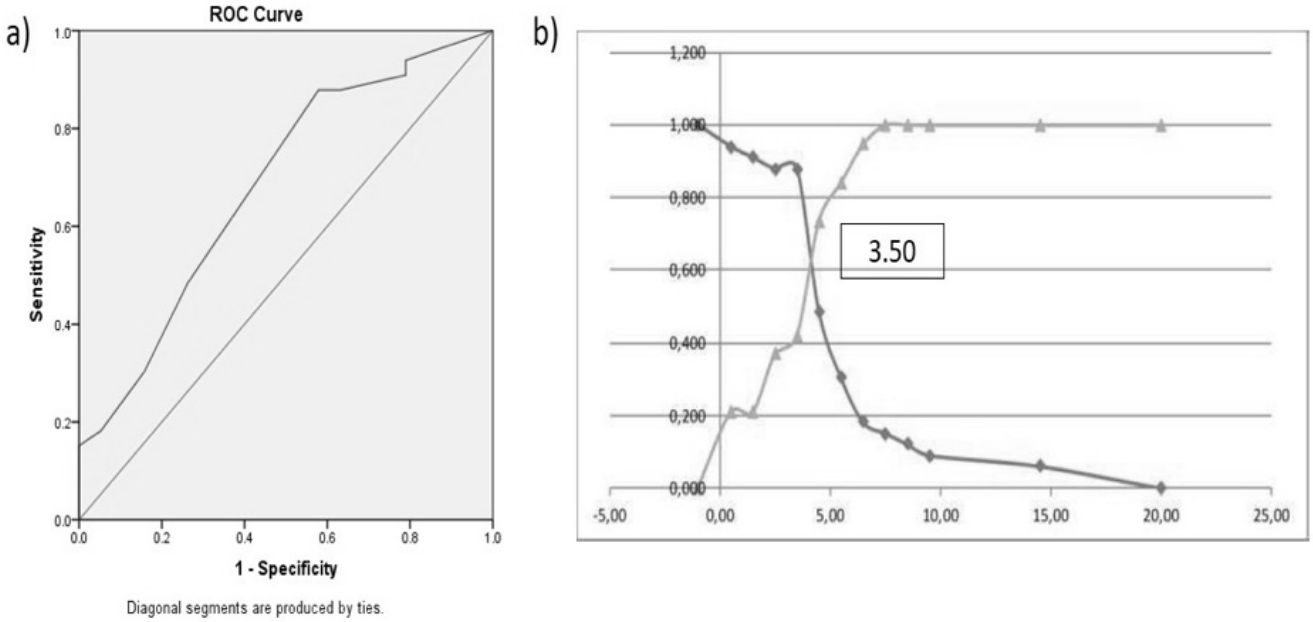

Fig. 2: ROC curve analysis to determine the cutoff value of TNS-PV scoring based on combination NCS with patient's symptoms. Fig. 2a blue line: diagonal line presenting AUC; Fig. 2a green line: reference line; Fig. 2b blue line: specificity; Fig. 2b green line: sensitivity.

Table 1: Clinical characteristic of ALL children.

Characteristic	**Value**
Sex n(%)	
• Male	31 (59.6)
• Female	21 (40.4)
Age group n(%)	
▪ < 10 years old	40 (76.9)
▪ ≥ 10 years old	12 (23.1)
Age, Mean ± SD (year old)	7.6±3.6
Age at diagnosis, Mean ± SD (year old)	6.7±3.7
Bone Marrow Aspiration Results n(%)	
▪ ALL-L1	49 (94.2)
▪ ALL-L2	3 (5.8)
Classification of ALL n(%)	
▪ Standard Risk	31 (59.6)
▪ High Risk	21 (40.4)
Nutritional status n(%)	
▪ Obesity and Overweight	4 (7.7)

▪ Well nourished	22 (42.3)
▪ Mild-moderate malnutrition	15 (28.8)
▪ Severe malnutrition	11 (21.2)
Complaints of peripheral neuropathy n(%)	
▪ Yes (Pain, weakness, paresthesia)	14 (26.9)
▪ No	38 (73.1)
Cumulative dose of Vincristine (mg/m^2), Median (minimum – maximum)	36 (13.5 – 52.0)
Duration of chemotherapy, Mean ± SD (month)	15.0 ± 6.1
Type of peripheral nerve lesion distribution based on NCS n(%)	
▪ Normal	4 (8.8)
▪ Demyelinating	15 (29.2)
▪ Axonal	6 (10.4)
▪ Axonal demyelinating	27 (51.6)
Motoric peripheral nerve distribution based on NCS n(%)	
▪ Median nerve	49 (94.2)
▪ Ulnaris nerve	50 (96.1)
▪ Tibialis nerve	52 (100)
▪ Peroneus nerve	52 (100)
Sensory peripheral nerve distribution based on NCS n(%)	
▪ Median nerve	48 (92.3)
▪ Ulnaris nerve	37 (71.2)
▪ Suralis nerve	42 (80.8)

an accumulative dose of vincristine greater than 5 mg, whereas motor peripheral neuropathy occurs at a dose of 30-50 mg.[15]

In this study, the mean cumulative dose of vincristine was 36 mg/m^2, with the highest dose being 52 mg/m^2. Vincristine is dose-dependent, therefore it is believed to cause dose-dependent motor-sensory axonal neuropathy. Almost all children showed normal clinical examination but electro-physiologically, there was peripheral neuropathy with a mean duration of chemotherapy for 15 months. A study found that 8% of ALL children experienced subclinical neuropathy after 5 weeks of vincristine.[16] This was probably due to incomplete myelination at a young age, because some nerves are more sensitive to neurotoxic chemotherapy agents.[17,18]

The prevalence of VIPN based only electrophysiological during chemotherapy was 100%, which is in line with several previous studies, in which the incidence range of VIPN during chemotherapy is 23.5 – 96%.[2,16,19,20] The electrophysiology of neuropathy in children suggests that motor neuropathy is predominant over sensory neuropathy. Incomplete myelination of motor nerves at a young age resulting in greater sensitivity of some nerves due to neurotoxic agents.[21] Our study showed that peripheral neuropathy in motor nerves was more prevalent than sensory nerves. Other research stated that vincristine causes motor nerve disorders than sensory nerves.[22] Although the electrophysiological picture is abnormal until 6 months after chemotherapy, clinical improvement are observed within 2-3 weeks after the end of vincristine chemotherapy.[23]

Table 3: TNS-PV Total Scoring based on NCS.

TNS-PV Scoring Total	NCS		Sensitivity	Specificity
	Positive (%)	Negative (%)		
≥ 3. 50	41 (78.8)	0 (0)	78.8%	Undefined
< 3.50	11 (21.2)	0 (0)		

*Data was presented as number (percentage)

One of the objective parameters used to determine peripheral neuropathy is NCS examination, which was carried out on 5 nerves, according to the order of occurrence of peripheral neuropathy, such as Tibialis, Peroneus, Medianus, Ulnaris, and Suralis. Peripheral motor neuropathy was more frequent than sensory, namely 99.9% motor and 76.0% sensory. The peripheral neuropathic disorders are characterized by a feeling of fatness, paresthesia, balance disorders, weakness of the tendon reflexes, and movement disorders.[23]

Electromyographic examination revealed that neuropathy was reported to be significant in children examined at 18 months of chemotherapy treatment (44.4%) compared with children that received chemotherapy for 19 – 36 months (20%). There was also an increase in the prevalence of neuropathy between the intervals of vincristine administration.[24] EMG is more invasive and painful because it is more difficult in children, therefore EMG is not recommended as the primary examination for diagnosing VIPN in children.[22]

The cutoff value of TNS-PV was 3.50, therefore the ALL children were divided into 2 categories. TNS-PV score < 3.5 are categorized as negative and ≥ 3.5 as positive. From this result, the positive VIPN was 78.8% of ALL children. All subjects had 100% positive results of NCS, therefore the cut off calculation obtained from the ROC analysis results are based on combination of NCS as the gold standard diagnosis with patients' symptoms Therefore, the diagnostic value of TNS-PV is related to the presence or absence of discomfort. This study is in line with research, where patients were significantly identified by having VIPN as much as 86% by using TNS-PV total score ≤ 4 when compared with the control group .[20] However, it is slightly different from other study, where the results reported that 128 ALL children that received vincristine therapy, and carried out longitudinal observations, obtained 78% of positive VIPN using TNS-PV score with patients aged 1 – 18 years.[2]

The limitation of this study is that there was low variation of the NCS value in the research subjects, even at TNS-PV value zero also showed positive NCS. This TNS-PV examination used interviews and examinations conducted by investigators under supervision, and ALL patients themselves were already suffering from their illness, which affects the outcome of the exam.

CONCLUSION

The TNS-PV cut off value of 3.5 has a sensitivity of 87.9% and a specificity of 42.1% which are used as the threshold score for screening before NCS examinations were carried out. Although TNS-PV cannot replace or match the NCS gold standard, TNS-PV might be used for diagnostic tool for the occurrence of VIPN in ALL children undergoing chemotherapy.

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Conception and design: Prastiya Indra Gunawan, Kartika Hardiyani, I Dewa Gede Ugrasena.
Collection and assembly of data: Prastiya Indra Gunawan, Kartika Hardiyani, I Dewa Gede Ugrasena.
Analysis and interpretation of data: Prastiya Indra Gunawan, Kartika Hardiyani.
Drafting of the article: Prastiya Indra Gunawan, I Dewa Gede Ugrasena
Critical revision of article for important intellectual content: Prastiya Indra Gunawan.
Statistical expertise: Prastiya Indra Gunawan.
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