## ORIGINAL

# RISK FACTORS OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN ACUTE LYMPHOBLASTIC LEUKAEMIA CHILDREN

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**Abstract : Objective : This study analysed Vincristine-induced peripheral neuropathy (VIPN) risk factors in Acute Lymphoblastic Leukaemia (ALL) children. Method : This cross-sectional study design was performed at Dr. Soetomo Hospital, Surabaya, Indonesia, from August to October 2019. It included ALL children, aged 4–18 years, undergoing the 2013 or 2018 ALL Indonesian Protocol of Chemotherapy, with a cumulative vincristine dose ≥ 12 mg/m². VIPN diagnosis is based on complaints, the Total Neuropathy Score Pediatric Vincristine (TNS-PV), and nerve conduction studies (NCS). The examined risk factors were sex, age, ALL classification, nutritional status, impaired liver function, and cumulative vincristine dose. Results : There were 52 ALL children : median age 7 years, 59.6% boys, 59.6% ALL standard risk, 44.2% experienced impaired liver function at initial ALL diagnosis. Based on a single parameter for diagnosis, 26.9% had VIPN based on complaints, 76.9% had it based on the TNS-PV, and 100% had it based on NCS. VIPN was diagnosed in 25% of children, with predominantly motor impairment and located in lower extremities. Impaired liver function is a risk factor for VIPN in ALL children (p = 0.046, prevalence ratio (PR) 2.84). Conclusion : Impaired liver function is a significant risk factor for VIPN in ALL children. J. Med. Invest. 68 : 232-237, August, 2021**

***Keywords*** **:** *risk factor, children, acute lymphoblastic leukaemia, vincristine, neuropathy*

## INTRODUCTION

Vincristine-induced peripheral neuropathy (VIPN) is a sensory, motoric, or autonomic nerve disorder following vincristine therapy (1). Vincristine is a chemotherapy agent that is used to treat acute lymphoblastic leukaemia (ALL) patients in the induction, intensification, and maintenance phases (2). Vincristine affects small and large nerve fibres and thus causes impaired sensory, motor, and autonomic function (1). For ALL patients who received vincristine, 13.8% experienced clinical peripheral neuropathy and 33.75% received a diagnosis based on electrophysiologic tests (3). Another study revealed 78% were diagnosed using the Total Neuropathy Score Pediatric Vincristine (TNS-PV) (1). Factors thought to contribute to the emergence of VIPN in children include age, sex, race, genetics, pharmacokinetics, vitamin B12 deficiency, drugs, and cumulative doses. However, until now there has been no report on a definite risk factor (4).

ALL is the most common lymphoid cell progenitor malignancy in children (1, 5-7). Each year, at least 3,000 children in the United States and 5,000 children in Europe are diagnosed with ALL (8). At the Dr. Soetomo Hospital (Surabaya, Indonesia), there were 143 children with ALL in 2017 and 114 children in 2018 (9). The survival rate has increased gradually from 10% in 1960 to 90% (7).

Long-term sequelae of VIPN leads to a quality of life reduction (1, 4, 10, 11). Recognising risk factors for VIPN will alert healthcare workers and families to detect early VIPN symptoms and thus ensure early treatment and, ideally, prevent a decrease in quality of life (1, 3). There have been limited studies of VIPN in Indonesia. The aim of this study was to analyse the VIPN risk factors in ALL children.

Received for publication September 29, 2020 ; accepted February 15, 2021.

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## MATERIALS AND METHODS

### *Patients*

The study was carried out on 4–18-years-old ALL children who underwent chemotherapy according to the ALL Indonesia 2013 or 2018 protocol, with a cumulative vincristine dose > 12 mg/m². Comprehensive informed consent and was obtained from a legal representative of each patient. Patients were excluded if they were uncooperative during nerve conduction studies (NCS) ; had a history of intracranial disorder, neuropathy, myopathy ; were septic ; had diabetes mellitus ; there was an incomplete medical record ; or refused to follow the procedure. All patients were undergoing the 2013 or 2018 ALL Indonesian Protocol of Chemotherapy maintenance phase treatment using intravenous Vincristine, intrathecal Methotrexate, and oral Dexamethasone.

### *Methods*

This cross-sectional study was conducted from August to October 2019, using consecutive sampling. The Ethical Committee in Health Research Dr. Soetomo Hospital Surabaya approved this study with internal review board number 1363/KEPK/VIII/2019. In every patient, anamnesis and physical examination were carried out at Pediatric Hematology Oncology Outpatient Clinic. TNS-PV and NCS were performed at the Medical Rehabilitation Outpatient Clinic. TNS-PV assessment includes subjective symptom, temperature, vibration, muscle tone, tendon reflex, and presence of autonomic and laryngeal neuropathy. NCS was performed using the Cadwell Sierra Wave EMG system (version 11.0.116). The examined risk factors were gender, age, ALL classification, nutritional status, impaired liver function, and cumulative vincristine dose ; these data were

obtained from medical records. Age was divided into ≤ 10 and > 10 years old. ALL classification was based on prognostic factor, categorised into standard and high risk (12). Nutritional status were considered from the time children were diagnosed with ALL, using the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) chart, categorised into obesity and overweight, healthy weight, and moderate and severe malnutrition (13). Liver function was considered from the time children were diagnosed ALL, assessed using aspartate transaminase (AST) and alanine transaminase (ALT). Stated as impaired liver function if AST and or ALT were above normal ranges based on gender and age (14). Diagnosis of axonal, demyelinating, and axonal demyelinating neuropathy were based on NCS result, by comparing patients' distal latency, action potential amplitude, and nerve conduction velocity with their normal range according to child's age and nerve type (15). Axonal neuropathy was established if NCS showed lower motor and sensory action potential amplitude. Demyelinating neuropathy was established if NCS showed slower distal latency and/or slower nerve conduction velocity. Axonal demyelinating neuropathy was established if NCS showed slower distal latency, lower motor and sensory action potential amplitude, slower motor and sensory nerve conduction velocity.

*VIPN diagnosis*

VIPN was diagnosed if the patients met all the following criteria :

1. Complaint of neuropathy (pain, paraesthesia, weakness, constipation, urinary retention, orthostatic hypotension) ;
2. TPN-VS score ≥ 4 ; and
3. NCS assessed by a medical rehabilitation specialist to indicate peripheral neuropathy.

*Statistical analysis*

SPSS version 21.0 was used for statistical analysis. Multivariate logistic regression was applied to evaluate data comparison between groups. Statistical significance was considered at a mean difference with $p < 0.05$.

## RESULTS

The study included 54 patients. Two patients were excluded because they refused the NCS examination. The subject characteristics are shown in Table 1.

This study was used three parameters in assessing peripheral neuropathy : neuropathy complaints, TNS-PV, and NCS ; Figure 1 presents the distribution for each parameter. Table 2 presents NCS parameters value which consist of distal latency, amplitude, nerve conduction velocity on each nerve. A VIPN diagnosis required all three criteria to be met. Based on single parameter, 26.9% had VIPN clinically (i.e. based on complaints), 76.9% based on TNS-PV, and 100% by NCS. Overall, 25% of the participants had VIPN.

VIPN was more frequent in females (33.3% vs 19.4%) and age > 10 years old (41.7% vs 20%). There was no significant relation between VIPN and sex ($p = 0.185$) or age ($p = 0.375$).

VIPN was more frequent in the ALL high risk group (33.3% vs 19.4%). Based on nutritional status, ALL children with a healthy weight had the highest incidence of VIPN (31.8%), followed by overweight and obesity (25%), then moderate and severe malnutrition (19.2%). There was no significant relation between VIPN and ALL classification ($p = 0.739$) or nutritional status ($p = 0.643$).

There was no significant relationship between VIPN and cumulative vincristine dose ($p = 0.581$). VIPN was more frequent in

Table 1. Characteristic data

| **Characteristic** | |
|---|---|
| Gender, n (%) | |
| • Male | 31 (59.6) |
| • Female | 21 (40.4) |
| Age groups, n (%) | |
| • < 10 years old | 40 (76.9) |
| • > 10 years old | 12 (23.1) |
| Age (years), median (min-max) | 7 (4 – 17) |
| Race, n (%) | |
| • Javanese | 44 (84.6) |
| • Maduranese | 8 (15.4) |
| Bone marrow aspiration result, n (%) | |
| • ALL-L1 | 49 (94.2) |
| • ALL-L2 | 3 (5.8) |
| ALL classification, n (%) | |
| • ALL standard risk | 31 (59.6) |
| • ALL high risk | 21 (40.4) |
| Nutritional status, n (%) | |
| • Obesity and overweight | 4 (7.7) |
| • Healthy weight | 22 (42.3) |
| • Moderate and severe malnutrition | 26 (50.0) |
| Concurrent medication, n (%) | |
| • Vincristine | 52 (100.0) |
| • Dexamethasone | 52 (100.0) |
| • Methotrexate | 9 (17.3) |
| Laboratory, median (min-max) | |
| • Hemoglobin (mg/dl) | 9.1 (1.3 – 14.5) |
| • Leukocyte (cell/mm$^3$) | 6,953.5 (640 – 279,940) |
| • Thrombocyte (cell/mm$^3$) | 33,520 (5,000 – 424,000) |
| • AST (U/L) | 34.5 (14 – 350) |
| • ALT (U/L) | 29.5 (6 – 233) |
| Impaired liver function, n (%) | |
| • Yes | 23 (44.2) |
| • No | 29 (55.8) |
| Peripheral neuropathy complain, n (%) | |
| • Yes | 14 (26.9) |
| • Pain | 4 |
| • Weakness | 9 |
| • Paresthesia | 1 |
| • No | 38 (73.1) |
| Cumulative dose of Vincristin (mg/m$^2$), median (min-max) | 36 (13.5 – 52.0) |
| Peripheral neuropathy based on NCS, mean % | |
| • Motoric vs sensory | |
| • Motoric | 100 |
| • Sensory | 76.5 |
| • Upper vs lower extremities | |
| • Upper | 88.6 |
| • Lower | 91.7 |
| • Type | |
| • Axonal | 9.6 |
| • Demyelinating | 20.7 |
| • Axonal demyelinating | 59.6 |
| Peripheral neuropathy, n (%) | |
| • Complain | 14 (26.9) |
| • TNS-PV | 40 (76.9) |
| • NCS | 52 (100.0) |
| • NCS and complain | 14 (26.9) |
| • NCS and TNS-PV | 40 (76.9) |
| • NCS, TNS-PV, and complain | 13 (25.0) |
| Vincristine Induced Peripheral Neuropathy, n (%) | |
| • Yes | 13 (25.0) |
| • No | 39 (75.0) |

ALL, acute lymphoblastic leukemia ; ALT, alanine transaminase ; AST, aspartate transaminase ; NCS, nerve conduction studies ; SD, standard deviation ; TNS-PV, total neuropathy score pediatric vincristine

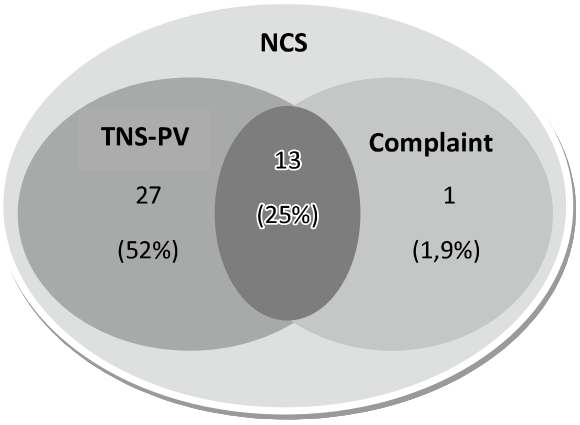


Figure 1. Frequency distribution of peripheral neuropathy based on NCS, TNS-PV, and complaint

Table 2. NCS characteristics of nerves

| **Median** | **Motoric** | | | **Sensory** | | |
|---|---|---|---|---|---|---|
| | **Latency (ms)** | **Amplitude (mV)** | **NCV (m/s)** | **Latency (ms)** | **Amplitude (μV)** | **NCV (m/s)** |
| Mean (±SD) | 3.4 (±0.8) | 6.2 (±2.3) | 53.2 (±7.3) | 2.7 (±0.7) | 26.8 (±14.5) | 40.6 (±7.4) |
| (Min – Max) | (1.9 – 7.5) | (1.5 – 12.7) | (38.0 – 72.0) | (1.7 – 6.3) | (2.3 – 61.3) | (17.0 – 61.0) |
| **Ulnar** | **Motoric** | | | **Sensory** | | |
| | **Latency (ms)** | **Amplitude (mV)** | **NCV (m/s)** | **Latency (ms)** | **Amplitude (μV)** | **NCV (m/s)** |
| Mean (±SD) | 3.0 (±1.3) | 4.7 (±1.9) | 58.9 (±7.6) | 2.5 (±1.0) | 21.0 (±11.7) | 38.7 (±12.1) |
| (Min – Max) | (1.3 – 7.8) | (1.3 – 8.4) | (40.0 – 75.0) | (0.6 – 6.9) | (0.0 – 64.0) | (0.0 – 74.0) |
| **Peroneal** | **Motoric** | | | | | |
| | **Latency (ms)** | **Amplitude (mV)** | **NCV (m/s)** | | | |
| Mean (±SD) | 4.3 (±1.6) | 1.5 (±1.1) | 43.8 (±13.6) | | | |
| (Min – Max) | (0.8 – 10.6) | (0.0 – 4.6) | (0.0 – 80.0) | | | |
| **Tibial** | **Motoric** | | | | | |
| | **Latency (ms)** | **Amplitude (mV)** | **NCV (m/s)** | | | |
| Mean (±SD) | 3.9 (±1.2) | 6.2 (±3.6) | 45.2 (±6.9) | | | |
| (Min – Max) | (0.5 – 8.1) | (0.1 – 14.7) | (32.0 – 56.0) | | | |
| **Sural** | **Sensory** | | | | | |
| | **Latency (ms)** | **Amplitude (μV)** | **NCV (m/s)** | | | |
| Mean (±SD) | 2.6 (±0.5) | 17.1 (±9.0) | 46.5 (±12.3) | | | |
| (Min – Max) | (1.3 – 4.8) | (1.5 – 41.2) | (29.0 – 92.0) | | | |

NCV, nerve conduction velocity

ALL children with impaired liver function (39.1% vs 13.8%) ; this relationship was significant (p = 0.046 ; prevalence ration (PR) 2.837). Table 3 presents risk factors of VIPN in ALL children.

## DISCUSSION

There is no consensus on the best method to diagnose VIPN based on the child's age (16). There are nine diagnostic methods of peripheral neuropathy used in children. One instrument is subjective pain reports based on perceptions that are assessed using facial expressions : the Wong–Baker FACES pain scale. Five objective assessments of peripheral neuropathy use physical examination : neurological examination, NCS, current perception threshold (CPT), tactile perception threshold (TPT), and vibration perception threshold (VPT). Three methods use subjective and objective assessment to evaluate the presence of peripheral neuropathy : Common Terminology Criteria for Adverse Events (CTCAE v3.0 or 4.0), the paediatric-modified Total Neuropathy Scale (ped-m TNS), and the TNS-PV (17).

In a study that involved 101 4–18-year-old ALL survivors, clinical peripheral neuropathy was found in 26.7% of individuals ; 68.3% would be diagnosed based on NCS. However, VIPN diagnosed based on both criteria was 15.8% (18). Another study diagnosed VIPN in 78% of patients using TNS-PV and only 44% of those who complained of pain (1). Jain studied VIPN

Table 3. Risk factors of VIPN in ALL children

| Risk factors | VIPN | | p value |
|---|---|---|---|
| | Yes (%) | No (%) | |
| Gender | | | |
| • Male | 6 (19.4) | 25 (80.6) | 0.185 |
| • Female | 7 (33.3) | 14 (66.7) | |
| ALL classification | | | |
| • Standard risk | 6 (19.4) | 25 (80.6) | 0.739 |
| • High risk | 7 (33.3) | 14 (66.7) | |
| Impaired liver function | | | |
| • Yes | 9 (39.1) | 14 (60.9) | 0.046* |
| • No | 4 (13.8) | 25 (86.2) | |
| Age | | | |
| • < 10 years old | 8 (20.0) | 32 (80.0) | 0.375 |
| • > 10 years old | 5 (41.7) | 7 (58.3) | |
| Nutritional status | | | |
| • Obesity and overweight | 1 (25.0) | 3 (75.0) | 0.643 |
| • Healthy weight | 7 (31.8) | 15 (68.2) | |
| • Moderate and severe malnutrition | 5 (19.2) | 21 (80.8) | |
| Cumulative dose of Vincristin (mg/m$^2$) | | | |
| • Mean (±SD) | 30.8 (±9.9) | 32.6 (±12.2) | 0.581 |
| (Min – Max) | (13.5 – 48) | (13.5 – 52) | |

*Significant for Multivariate logistic regression. ALL, acute lymphoblastic leukemia ; SD, standard deviation

using three parameters : clinical, TNS-PV, and electrophysiology. Based on a single parameter, 13.8% had VIPN clinically, 33.8% by TNS-PV, and 33.8% by electrophysiology. Only 6.3% had VIPN based on all three parameters (3). In Indonesia, a study in ALL children showed 0.3% had VIPN clinically (19). In this study, VIPN was diagnosed in 25% patients, based on complaints of neuropathy, TNS-PV, and NCS.

In agreement with previous studies, VIPN in this study was more frequent in females (20, 21). Another study stated that VIPN was more frequent in males (22). Seven studies showed no significant relationship between sex and VIPN (1, 11). Anghelescu studied 498 ALL children and divided their age into four groups (1–5, 6–10, 11–15, and 16–20 years). The highest incidence of VIPN was in the 16–20-year-old group (40%), and the lowest was in the 1–5-year-old group (30.6%). This phenomenon may be due to age-related factors, but it was not statistically significant (11).

In previous study, the VIPN incidence was significantly higher in the ALL high risk group (75.4% vs 24.6%, $p = 0.019$). The authors hypothesised that the higher cumulative vincristine dose in the ALL high risk group (48 vs 33.36 mg/m$^2$) explained this increased VIPN incidence (18).

Adequate and constant nutrition supports optimal peripheral nerve function. ALL children often suffer from malnutrition and nutrient deficiency, while symptoms occur at the terminal stage of malnutrition. Nutrients that are thought to play an important role in optimal nerve function are vitamin E, vitamin B12, thiamine, niacin, pyridoxine, copper, and folic acid (23, 24). Jain (25) found that there was no significant difference in the level of alpha tocopherol, vitamin B12, and folic acid serum ($p \geq 0.15$) in ALL children with or without neuropathy ($n = 80$) (25). Although vitamin B12 and other micronutrient deficiencies were associated with the incidence of neurotoxicity in the general population, vitamin levels were not significantly different in patient with or without VIPN (26).

Liver transaminases are considered to be the most sensitive tests for hepatocellular necrosis (hepatitis). ALT is a more specific marker than AST for liver injury because it is mostly found in liver tissue, localised to the hepatocyte cytosol. Although ALT isoenzymes are expressed in many tissues, elevated serum ALT activity is considered the 'gold standard' clinical marker for liver injury in humans. AST is more broadly distributed in other extrahepatic sites, including heart, skeletal muscle, kidney, brain, and red blood cells (27). Hepatic infiltration usually occurs with subsequent hepatomegaly and often in conjunction with splenic involvement. ALL in paediatric patients presents with hepatomegaly and liver involvement in 68% of the cases and is one of the most frequent presenting symptoms (28). Liver involvement mostly appears to be mild and asymptomatic, but a post-mortem study found liver infiltration in more than 95% of ALL patients (29). Liver involvement in ALL at diagnosis is due to direct portal and sinusoidal infiltration by leukaemic cells, with an elevation in hepatic transaminases a consequence of the hepatocellular necrosis. Perhaps further injury is mediated by acetaminophen, which is often used to treat underlying fever that is present at the time of a leukaemia diagnosis (27). Vincristine is distributed through passive diffusion into organs and metabolised in the liver ; it has efficacy against tumour cells and toxicity against neurons (26). Vincristine is mainly excreted through bile and faeces ; only a small amount is excreted by the kidneys (30).

Cytochrome P450 3A (CYP3A), found in the liver, is a subfamily of important enzymes in drug metabolism. CYP3A-mediated vincristine metabolism leads to neurotoxicity. Vincristine is mainly metabolised by CYP3A4 – the main metabolic enzyme

of the CYP3A family – and CYP3A5. Genetic polymorphism of CYP3A5 expression affects individual clinical variabilities related to vincristine efficacy. More than 70% of African Americans have at least one CYP3A5*1 allele that facilitates active CYP3A5 expression. The CYP3A5*1 allele is only found in 10%–20% of Caucasians. In people with the CYP3A5*1 allele, CYP3A5 represent more than 50% of CYP3A in liver microsomes (26). In another study, CYP3A5 was more frequently expressed in livers of African Americans (60%) compared with Caucasians (33%) (31). Several studies in specific genotypes related to race revealed that African Americans are more effective in vincristine metabolism, and hence they exhibit lower vincristine toxicity (16). Vincristine toxicity increases along with impaired liver function (32), which negatively affects vincristine metabolism and excretion (33).

A previous study found a significant relationship between the cumulative vincristine dose and VIPN. The authors divided ALL children into two groups and gave them a different chemotherapy protocol. The first group used vincristine 2 mg/m$^2$/dose, while the second group used vincristine 1.5 mg/m$^2$/dose. The occurrence of VIPN in this study was thought to be due to higher dose per time administration, so it was indirectly related to cumulative doses (20). The amplitude of peroneal nerve potential action, ulnar, and median sensory decreased during vincristine therapy, but there was neither a significant relationship to the vincristine cumulative dose nor an effect from vincristine therapy on the nerve conduction velocity (22).

There are a few limitations of this study. First, genetic factors were neither checked nor included as a cofounding factor. Second, NCS was not performed before the chemotherapy began. In conclusion, impaired liver function was a risk factor of VIPN in ALL children, while sex, age, ALL classification, nutritional status, and cumulative vincristine dose were not.

## CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest in this study.

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