

Epidemiological Characteristics and 3-year Overall Survival Outcome of Nasopharyngeal Cancer in Central Java: A Single Institution Retrospective Study

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ABSTRACT

Background: Nasopharyngeal cancer (NPC) has a high incidence and mortality rate in Indonesia, indicating poor survival outcomes. We aimed to evaluate the survival rate of NPC patients and the influence of specific underlying epidemiological characteristics on the overall survival (OS) rate of NPC patients.

Methods: We reviewed the medical data from Dr. Kariadi General Hospital's clinical registry system for all newly diagnosed NPC patients between January and December 2018. We retrieved NPC patients' medical record data that met our inclusion/exclusion criteria. The overall survival rate (OS) was estimated using the Kaplan-Meier method. Between-group stratified three-year OS comparisons were conducted using weighted log-rank tests. All statistical analysis was performed in R statistical software.

Results: A total of 50 NPC patients were included in the study. Majority of NPC patients were diagnosed in younger age group (58.0%). Male NPC patients dominated this study (74.0%). NPC patients were mostly diagnosed at the advanced stage (76.0%). Nonkeratinizing histology types were frequently found in the study (82.0%). NPC patients achieved a desirable better performance status (78.0%) and had no comorbidities (74.0%). Most NPC patients demonstrated a complete response to therapy (58.0%). The mean follow-up was 26.36 ± 9.5 months and drop-out rate was 18.0%. The three-year OS was 60.8%. Age, sex, stage, histological classification, performance status, comorbidity, therapy response, and therapy drop-out stratified OS did not statistically differ among NPC patients.

Conclusions: We found a satisfactory NPC three-year OS. The underlying epidemiological characteristics did not significantly influence the NPC patients' three-year OS.

INTRODUCTION

Nasopharyngeal cancer (NPC) is the world's most prevalent head and neck malignancy [1]. NPC incidence is unevenly distributed across geographic regions worldwide, where it is endemic to Southern China, Northern Africa, and Southeast Asia [2]. In Indonesia, the NPC incidence rate is ranked fifth highest after breast (16.6%), cervix (9.2%), lung (8.8%), and liver cancer (5.4%). The NPC mortality rate is also ranked fifth, after lung (13.2%), breast (9.6%), cervix (9.0%), and liver cancer (8.9%) [3]. A high incidence and mortality rate reflect poor cancer outcomes relative to the incidence of the entire NPC population in Indonesia [4]. This data further

indicates areas for targeting interventions related to access to screening and treatment or clinical management to improve NPC patient survival in Indonesia.

NPC is usually diagnosed at an advanced stage due to unspecific symptoms, tumor anatomic location, or a lack of health-seeking behavior, which further contributes to poor NPC patients' survival rates [5]. The survival rate is an imperative and most commonly used outcome measure of cancer diagnosis and treatment [6]. In addition, other epidemiological characteristics, such as age at diagnosis, sex, tumor histology, comorbidity, and therapy response, also influence the survival rate in NPC patients [7]. Evaluating epidemiological characteristics or factors that underlie survival rates in NPC patients

is critical for NPC control, treatment/clinical management evaluation, and improving health outcomes [8].

The NPC epidemiological study indicates a high variation in distribution across regions, races, and ethnicities within a country [9,10]. On the other hand, Indonesia's national cancer registry is only sampled from 10 cities/districts, covering only 5% to 10% of the population in each city/district [11]. That design might lead to unrepresentativeness, introducing bias and failing to capture variation in distribution across regions, races, or ethnicities, especially for NPC epidemiology studies [12]. Some previous epidemiological studies on NPC used hospital-based cancer registries, in which most NPC patients are managed by default in tertiary healthcare facilities, such as Dharmas Cancer Hospital and Cipto Mangunkusumo National General Hospital [13,14]. The nature of vertical referral in cancer management allows hospitals in our national tertiary healthcare system to pool and include NPC patients from different districts/cities within regions, races, and ethnicities within their regional service area. Therefore, using a hospital-based medical record registry for cancer epidemiology studies seems more representative and methodologically rigorous to capture NPC epidemiological variation in region, race, and ethnicity, especially in Indonesia, where the national cancer registries have a representative bias. In addition, a similar approach was taken by the International Agency for Research on Cancer (IARC) with a combined analysis of the Cancer Information (CIN) databases to capture NPC disparity in the global scope [15]. On the other hand, some hospitals serving regions with a particular ethnic homogenous majority, such as Central Java, Yogyakarta, and East Java, are still contributing to capturing inter-regional differences within the country irrespective of racial and ethnic variation distribution [16].

Despite the high incidence of NPC in Indonesia, there is still an insufficient need for a comprehensive report on epidemiological characteristics and their influence on the survival rate of NPC patients from hospitals in tertiary healthcare in Indonesia. In the present study, we evaluate the epidemiological characteristics and their influence on the survival rate of NPC patients in our hospital.

METHODS

Setting

Dr. Kariadi General Hospital was a national tertiary referral hospital in Central Java. Based on the national health system, our hospital received a vertical referral from all hospitals across Central Java Province. Our hospital was also equipped to provide comprehensive oncology management in the region.

Study Design

In this retrospective survival analysis, we specified several factors to consider: accrual time, follow-up time,

event, and survival rate estimation. We set accrual time for one year, from January to December 2018. We followed the patients diagnosed with NPC during this accrual period for the subsequent three years. In addition, we also included patients referred to our hospital for NPC management as long as they were diagnosed during the accrual time frame.

In our study, we defined the event as a patient's death. We did not specify whether the cause of death was due to NPC or other factors; therefore, we estimated the overall survival (OS) rate [17]. Furthermore, we defined the starting point of the OS rate as the date of diagnosis. This survival starting point would have given us a better OS estimate, as most oncology patients in developing countries, including Indonesia, might have started treatment relatively late or delayed treatment after diagnosis [18,19].

Participants

We identified and included newly diagnosed NPC patients in our hospital during accrual time. We also included the referred NPC patients to our hospital, as long as they were diagnosed during the accrual time of the study. We excluded NPC patients who were under 18 years old at NPC diagnosis. In addition, we excluded patients who had inadequate or incomplete medical record data (**Figure 1**).

Data sources and measurements

We retrieved the data from Dr. Kariadi General Hospital's clinical registry system. We exclusively compiled and reviewed medical record data for the 2018-year NPC patient cohort. We took measurements from our medical data, including date of birth, sex, primary tumor size (T), lymph node involvement (N), distant metastasis (M), comorbidity, performance status, therapy response, latest hospital visit, vital status, and time. We joined medical record data with patients' histopathological classifications from the pathological anatomy report database.

The age at diagnosis was measured by subtracting the date of diagnosis from the date of birth. Clinical cancer staging in this study was aligned with the 8th American Joint Committee on Cancer (AJCC), in which T, N, and M criteria were explained elsewhere [20]. We categorized the histopathological differentiation according to the World Health Organization (WHO) classification system into two types: keratinizing squamous cell carcinoma (Type I) and nonkeratinizing squamous cell carcinoma, which encompassed nonkeratinizing carcinoma, including differentiated (Type II) and undifferentiated (Type III) nonkeratinizing carcinoma. We recorded all comorbidities enlisted in the Adult Comorbidity Evaluation (ACE), such as hypertension, diabetes mellitus, cardiovascular disease, azotemia, and infections, but not the scoring system [21]. We used the Eastern

Cooperative Oncology Group (ECOG) to measure patients’ performance. ECOG performance criteria might be explained elsewhere [22]. Therapy responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST). Further explanation of the RECIST evaluation guidelines might be found elsewhere [23].

Patients’ vital status during the follow-up period included alive, dead, and lost to follow-up. We did not specify the cause of death. All possible vital statuses in the study were alive, whether patients had tumor progression or regression, loss of follow-up, or death. [17] Patients who lost follow-up or were alive after three subsequent years were considered right-censored data [24].

Treatment and follow-up

All patients received NPC treatments according to the national nasopharyngeal cancer management guideline [25]. The guideline also explained follow-up and treatment evaluation. The management and follow-up guidelines could be found elsewhere.

Study size

A minimum calculated sample in this study was measured based on some statistical parameters, including alpha, beta, survival rate, and sample size ratio from previous studies [26]. We set alpha and beta at 0.05 and 0.1, respectively. We used survival data from Avdulla et al. [27] for further sample size determination in this study. The minimum calculated sample for this study was 40 patients.

Statistical analysis

Statistical analysis was conducted using the open-source RStudio Statistical Software version 2023.03.1 (R Foundation for Statistical Computing, Vienna, Austria) [28]. A descriptive analysis was conducted to summarize and understand the patient data. Quantitative variables were summarized using measures of central tendency (e.g., mean and median) and dispersion (e.g., standard deviation and interquartile range (IQR)). The frequencies or percentages of ordinal and nominal qualitative variables were also reported. The Kaplan-Meier (KM) method was used to estimate the survival rate using the “survival” package, and the KM curve was visualized using the “survminer” package [29=31]. Moreover, we also included the table of the number of NPC patients at risk since it robustly guided KM curve test interpretation and mitigated statistical pitfalls [24].

On the other hand, OS-stratified specific epidemiological characteristics were calculated and compared between the groups using weighted log-rank tests (e.g., the Gehan-Breslow and Peto-Peto tests), as the unweighted log-rank test was sensitive to the difference in late time [32,33]. Gehan-Breslow weighted the information at the beginning of the survival curve, where the number of individuals at risk was high, giving early failures greater weight than later failures [34]. In addition, Peto-Peto tests emphasized the n-th failure time by the survival estimate calculated over all groups combined (for further explanation and formulation, see [34]). The tests were performed using the “survminer” package [31]. The significance level was set at a p-value ≤0.05 (double-sided).

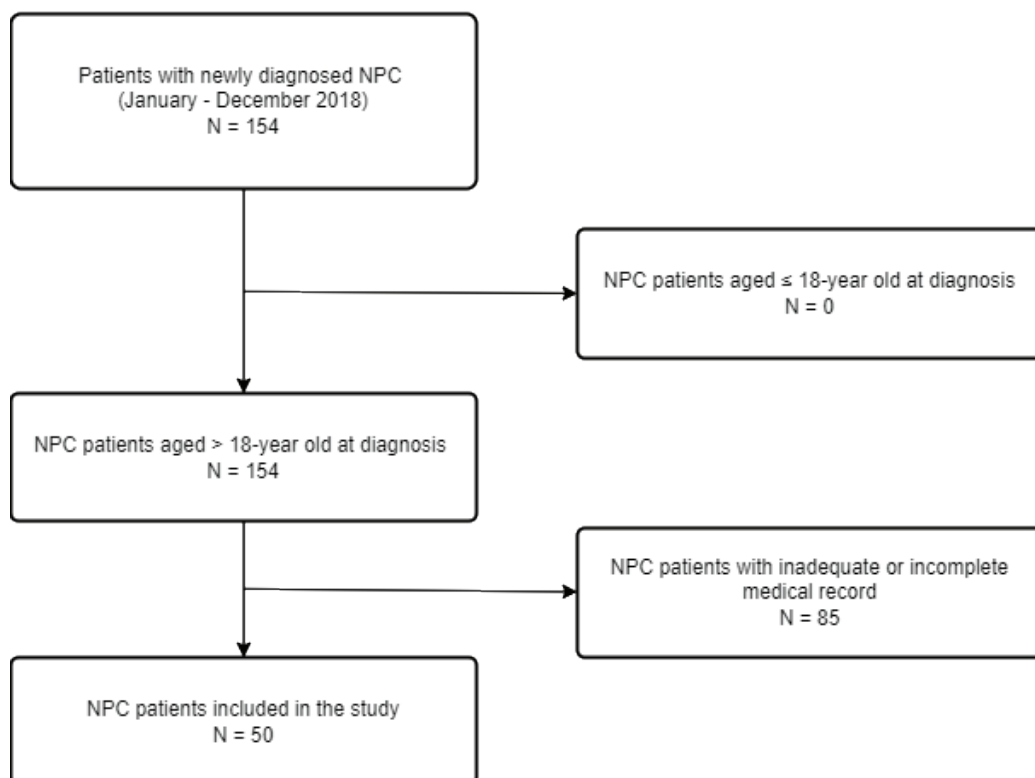


Figure 1. Flowchart of patient selection for analysis

RESULTS

Patients characteristics

A total of 50 patients who met our inclusion/exclusion were included in the analysis. The mean of the patient's age was 46.64 ± 13.8 years, and the median was 47.00 (IQR 37–56.5). The youngest and oldest patients were 18 and 74 years old, respectively. Most of our patients were male (74.0%). Most of our patients were diagnosed at an advanced stage (76.0%), and 31.6% of those at an advanced stage had distant metastasis. Most of those NPC metastasized to bone (66.7%), lung (16.7%), liver (8.3%), and thyroid (8.3%). Most of our patients had no comorbidities (74.0%). Most of our patients were histologically classified as nonkeratinizing carcinoma (82.0%). Almost all patients performed well in daily life (78.0%). Most of our patients showed a complete therapy response (58.0%). Most of our patients in the study demonstrated remarkable compliance, with a drop-out rate of 18.0%. All other patients' characteristics are shown in **Table 1**.

Survival analysis

The mean follow-up time from diagnosis in the study was 26.36 ± 9.5 months, while the median follow-up time was 24 (IQR 19.2–33.0) months. The shortest follow-up in the study was ten months. The one-year, two-year, and three-year OS of the 50 patients with NPC were 98.0%, 84.2%, and 60.8%, respectively (**Figure 2**).

Stratified OS

Age

Patients' age at NPC diagnosis fell into two categories: <50 or ≥ 50 years old. Patients younger than 50 indicated one-year, two-year, and three-year OS of 100.0%, 87.3%, and 64.6%, respectively. On the other hand, patients who were 50 years old or older indicated one-year, two-year, and three-year OS of 95.2%, 79.0%, and 51.9%, respectively. We could not determine the median OS for both age groups (**Figure 3**). No significant statistical differences in OS were observed between age groups (**Table 2**).

Sex

Male NPC patients indicated one-year, two-year, and three-year OS of 100.0%, 88.8%, and 58.9%, respectively. On the other hand, female NPC patients demonstrated one-year, two-year, and three-year OS at 92.3%, 72.5%, and 72.5%, respectively. We could not determine the median OS for both age groups (**Figure 3**). No significant statistical differences in OS were observed between males and females (**Table 2**).

Stage

NPC patients diagnosed in the advanced stage demonstrated one-year, two-year, and three-year OS of 97.4%, 79.9%, and 58.4%, respectively. On the other hand, patients diagnosed in the early stage demonstrated one-year, two-year, and three-year OS at 100.0%, 91.7%, and 66.8%, respectively. We could not determine the median OS for both age groups (**Figure 3**). No significant statistical differences in OS were observed between groups of NPC stages at diagnosis (**Table 2**).

Histological classification

NPC patients with keratinizing squamous cell carcinoma (type I WHO) demonstrated one-year, two-year, and three-year OS of 100.0%, 87.5%, and 87.5%, respectively. On the other hand, patients with nonkeratinizing squamous cell carcinoma indicated one-year, two-year, and three-year OS of 97.6%, 85.0%, and 59.9%, respectively. We could not reveal the median OS for both NPC histological group types (**Figure 3**). No significant statistical differences in OS were found between these two groups of NPC histological classification (**Table 2**).

Performance status

NPC patients with good performance status (ECOG scale 0–1) demonstrated one-year, two-year, and three-year OS of 97.4%, 83.9%, and 59.9%, respectively. Contradictorily, patients with unfavorable performance status (ECOG scale >1) indicated one-year, two-year, and three-year OS of 100.0%, 85.7%, and 64.3%, respectively. We could not determine the median OS for both performance status groups (**Figure 3**). No significant statistical difference in OS was found between both performance status groups (**Table 2**).

Comorbidity

NPC patients without comorbidity indicated one-year, two-year, and three-year OS of 97.3%, 85.6%, and 61.1%, respectively. Contrarily, patients with at least one comorbidity demonstrated one-year, two-year, and three-year OS of 100.0%, 80.8%, and 64.6%, respectively. We could not determine the median OS for patients with and without comorbidity (**Figure 3**). No significant statistical difference in OS was detected between groups of patients with and without comorbidity (**Table 2**).

Therapy response

NPC patients with partial therapy response demonstrated one-year, two-year, and three-year OS of 95.2%, 87.9%, and 56.5%, respectively. On the other hand, patients with complete response therapy indicated one-year, two-year, and three-year OS of 100.0%, 82.9%, and 63.2%, respectively. We could not demonstrate the median OS for both response therapy

Table 1. Patients' characteristics

Variable	N (%)
Age (years)	
<50	29 (58.0)
≥50	21 (42.0)
Sex	
Female	13 (26.0)
Male	37 (74.0)
Stage	
Early	12 (24.0)
Advanced	38 (76.0)
Histological Classification	
WHO Type I	9 (18.0)
WHO Type II–III	41 (82.0)
Performance Status	
ECOG >1	11 (22.0)
ECOG ≤1	39 (78.0)
Presence of Comorbidities	
0	37 (74.0)
≥1	13 (26.0)
Therapy Response	
Partial	21 (42.0)
Complete	29 (58.0)
Therapy Drop-out	
Yes	9 (18.0)
No	41 (82.0)

ECOG: Eastern Cooperative Oncology Group,
 WHO: World Health Organization
 WHO Type I: Keratinizing squamous cell carcinoma,
 WHO Type II: Differentiated nonkeratinizing carcinoma,
 WHO Type III: Undifferentiated nonkeratinizing carcinoma

Table 2. Stratified OS

Variable	Overall Survival			P-value
	One-year (%)	Two-year (%)	Three-year (%)	
Age				
<50	100.0	87.3	64.6	0.37‡
≥50	95.2	79.0	51.9	
Sex				
Female	92.3	72.5	72.5	0.24†
Male	100.0	88.8	58.9	
Stage				
Early	100.0	91.7	66.8	0.41‡
Advanced	97.4	79.9	58.4	
Histological Classification				
WHO Type I	100.0	87.5	87.5	0.57†
WHO Type II–III	97.6	85.0	59.9	
Performance Status				
ECOG >1	100.0	85.7	64.3	0.86‡
ECOG ≤1	97.4	83.9	59.9	
Presence of Comorbidities				
No	97.3	85.6	61.1	0.32†
Yes	100.0	80.8	64.6	
Therapy Response				
Partial	95.2	87.9	56.5	0.46‡
Complete	100.0	82.9	63.2	
Therapy Drop-out				
Yes	100.0	83.3	55.6	0.50‡
No	97.6	84.4	62.0	

† Gehan-Breslow test
 ‡ Peto-Peto test
 ECOG: Eastern Cooperative Oncology Group,
 WHO: World Health Organization
 WHO Type I: Keratinizing squamous cell carcinoma, WHO Type II:
 Differentiated nonkeratinizing carcinoma, WHO Type III:
 Undifferentiated nonkeratinizing carcinoma

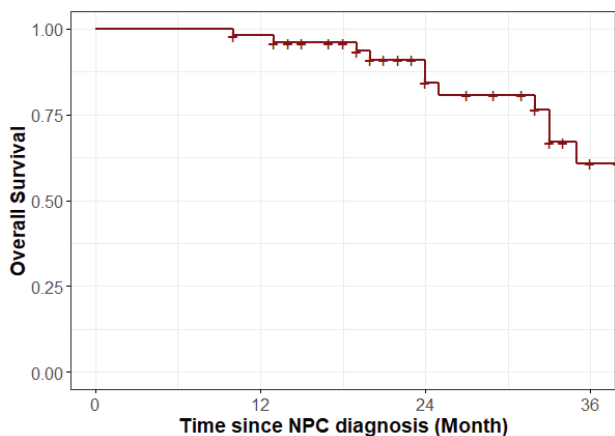


Figure 2. Three-year overall survival

groups (**Figure 3**). No significant statistical difference in OS was observed between response therapy groups (**Table 2**).

Therapy drop-out

NPC patients who dropped out of cancer therapy demonstrated one-year, two-year, and three-year OS of 100.0%, 83.3%, and 55.6%, respectively. Contradictorily, patients who did not drop out of cancer therapy demonstrated one-year, two-year, and three-year OS of 97.6%, 84.4%, and 62.0%, respectively. We could not demonstrate the median OS for both therapy drop-out groups (**Figure 3**). No significant statistical difference in OS was observed between drop-out and non-drop-out patients (**Table 2**).

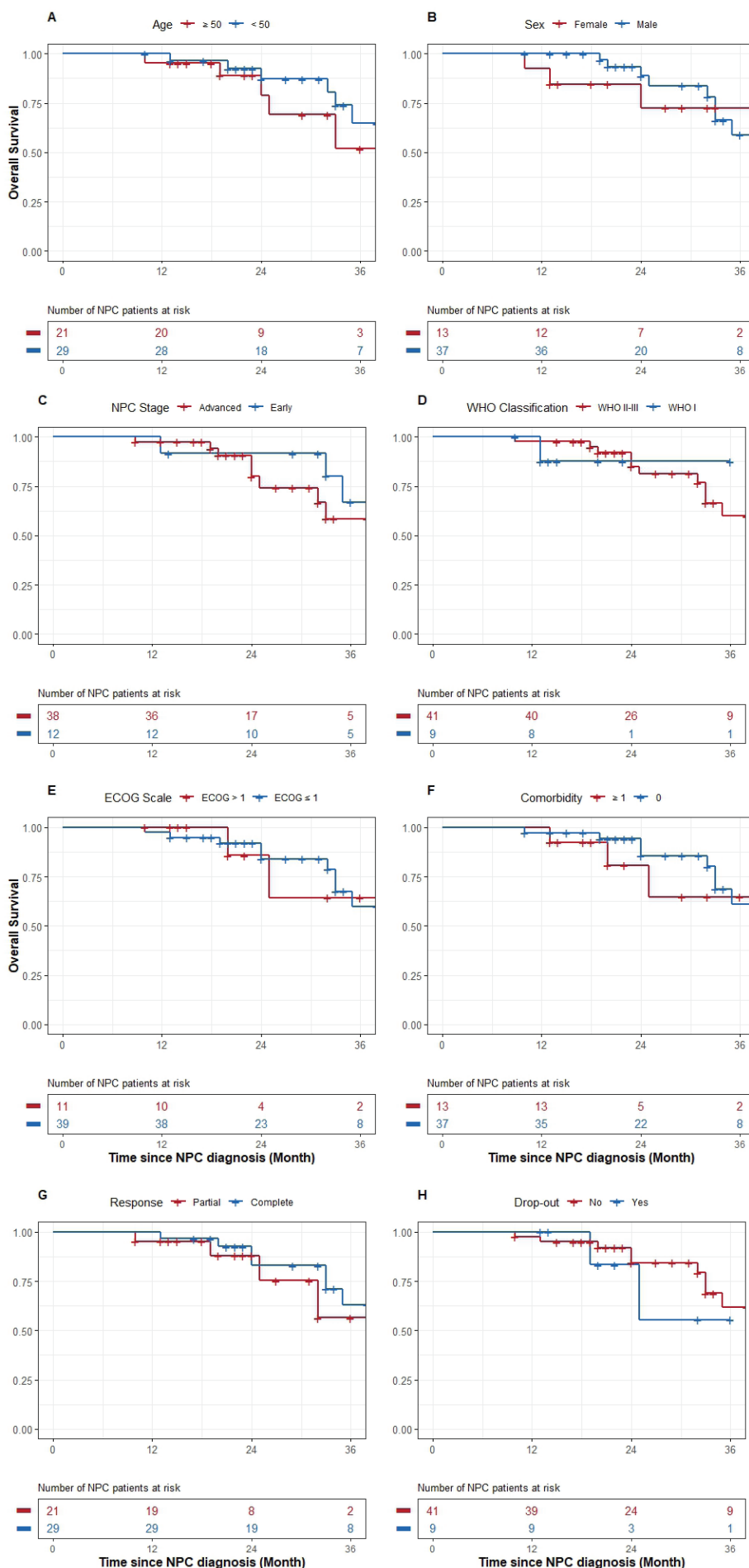


Figure 3. Stratified three-year overall survival

- (A) Age-stratified three-year OS;
- (B) Sex-stratified three-year OS;
- (C) Stage-stratified three-year OS;
- (D) Histological type-stratified three-year OS;
- (E) Performance status-stratified three-year OS;
- (F) Comorbidity-stratified three-year OS;
- (G) Therapy response-stratified three-year OS;
- (H) Therapy drop-out-stratified three-year.

DISCUSSION

This study presented a relatively high three-year OS, as we did not observe the median three-year OS. The median OS will be observed when 50% of the sample patients in the study have died [35]. In a previous study, Reffai et al. [36] did not demonstrate median OS, even in ten- and five-year OS estimates, respectively. On the other hand, Avdulla et al. [27] and Hutajulu et al. [37] demonstrated the observed median OS among NPC patients. Hutajulu et al. [37] indicated that the observed median survival median was 31.08 months. On the other hand, Avdulla et al. [27] did not explicitly imply observed median OS in their study. The reason that both studies were not available to estimate observed median OS was due to a shortage of follow-up. The median OS estimate required a long follow-up period as median OS was observed when 50% of the sample died [35]. Statistical bias in both studies might also be responsible for this phenomenon due to excessive right censoring points [24]. The interplay of these two conditions in the study hindered median OS estimation. Small sample bias might not have a significant contribution to median OS in a short follow-up study [38].

The early-stage NPC patients exhibited a better three-year survival rate than the advanced stage but were not statistically significant. Some previous studies indicated that early-stage NPC patients had a better OS, even though it was not statistically significant. Reffai et al. demonstrated that early-stage NPC patients had better five-year OS compared to their counterparts (advanced and metastatic stages) [36]. In addition, Avdulla et al. [27] indicated that NPC patients who were diagnosed with stage I and stage II had better ten-year OS than stage III patients but not stage IV patients, even though this was not statistically significant. Furthermore, Liu et al. [39] also found that early-stage NPC patients had better five-year OS than their counterparts (III, IV, and unknown groups). Contradictorily, Hutajulu et al. [37] indicated that early-stage NPC patients (stage I-II) had a significantly better five-year OS than advanced-stage (stage III-IVB) and metastatic stage (stage IVC). Moreover, Zhu et al. [40] revealed that early-stage NPC patients (stage I-II) had a significantly better ten-year OS than advanced-stage patients (stage III-IVB).

Early-stage cancer had better OS due to modest development, progression, and invasion [41]. Diagnosis and management of early-stage cancer would benefit from anticancer agents reaching localized benign tumor cells in the primary site [42]. In addition, early-stage cancer cells also had relatively more tumor homogeneity than heterogeneity [43]. They tended to have identical collections of cells harboring common molecular signatures and uniform sensitivity to specific chemotherapy agents [43]. Sensitive tumor cells would respond well to chemotherapy, resulting in a high

locoregional control rate and a reduction in tumor size [44]. In addition, a cancer diagnosis in the early stages alone was insufficient to provide better survival for cancer patients. A delay or absence in definitive cancer treatment initiation would hinder the benefit of early-stage diagnosis as cancer could progress to an advanced or metastatic stage that was hard to manage [41,42]. Cone et al. [45] demonstrated that delayed time-to-treatment initiation (TTI) reduced five- and ten-year OS. In addition, a meta-analysis study revealed a four-week delay in TTI, increasing mortality significantly in some types of cancer [46]. A barrier to cancer care might adversely affect patients' survival, even if diagnosed at an early stage.

The NPC WHO type-I (keratinizing SCC) histology group indicated a better three-year OS than other histology types (nonkeratinizing carcinomas), though not statistically significant. This result might be even more complicated as statistical pitfalls were applied in this study (explained in another section). There were comparable and opposite previous studies, even at various statistical significance levels. Ou et al. [47] exposed that the keratinizing SCC group had a better statistically significant five-year OS than nonkeratinizing carcinomas. Contrarily, a more extensive study on the influence of NPC histological type found that the nonkeratinizing carcinoma group had a better statistically significant five-year OS than keratinizing SCC [48]. On the other hand, an extended histology group classification had more conflicting results, demonstrating that WHO type III had better OS, even with a convergent significance level [49]. However, a survival analysis from an extended follow-up, multiracial nationwide cohort found that WHO type-II, III, and I histology classifications had better 25-year OS, respectively [50].

The WHO type II group had a better OS as it was well-differentiated and nonkeratinized [51]. Keratinization in squamous cell carcinoma has resulted from long-term carcinogenic mechanical stress exposure, such as cigarettes and alcohol [52]. This exposure would lead the normal cell to process post-translational modifications and protein interactions, which further played a different functional role in tumorigenesis and drug responsiveness [53]. Keratinized tumor cells also had protective or minimal effects on chemotherapy agents or ionizing radiation that prevented their programmed cell death [51,54]. On the other hand, nonkeratinizing carcinomas were caused by viral oncogenes rather than mechanical stress exposure [52]. These cancer types were further classified based on their degree of differentiation heterogeneity: well-differentiated and undifferentiated. The undifferentiated tumor cells had more aggressive tumor behavior (highly proliferative and invasive), which led to an advanced or metastatic cancer stage and OS disparity [54,55]. In addition, tumor histological types were independent of tumor heterogeneity [56].

NPC patients with complete response therapy had a better three-year OS than their counterparts, but it was not statistically significant. Several previous studies had comparable findings to ours, even at divergently significant levels. Dwijayanti et al. and Korkmaz et al. found that NPC patients with complete responses had a significantly better five-year OS than patients with partial responses [57,58]. Partial tumor response results from tumor heterogeneity during cancer development due to genetic, transcriptomic, epigenetic, and/or phenotypic changes [59,60]. Tumor heterogeneity entailed the diverse distribution of tumor subpopulations across different disease sites or within a single disease site of a tumor, which had a diverse collection of cancer cells with distinct molecular signatures and different levels of treatment sensitivity [43]. Tumor heterogeneity led to non-uniform responses that reduced therapeutic efficacy [61]. Targeting predominant sensitive subclones and various subsets of drug-tolerant and drug-resistant cells might be the finest approach to the most durable response [62]. Furthermore, more advanced tumor heterogeneity could lead to resistance to therapeutic modalities and hinder personalized or targeted treatment, as temporal and between-tumor heterogeneity might occur during tumor progression and development [59,60,62]. On the other hand, complete responders with minimal or non-detectable disease burden post-treatment were also susceptible to drug-resistant progression in longer follow-up due to minimal residual disease (MRD) upon initial remarkable tumor response and potential comeback as recurrence disease [63].

The younger age group of NPC patients (<50 years old) indicated better three-year OS than their counterparts, even though it was not statistically significant. Some previous studies shared similar results to ours. Reffai et al. indicated no statistical difference in five-year OS among some age groups (<30, 30–50, 51–70, and >70 years old), even though younger age groups had better OS than their respective counterparts [36]. Zhu et al. [40] evaluated the ten-year OS among younger age range groups (19–30 years) and found that the OS did not differ significantly across age range groups (≤ 19 vs. 20–26 vs. 27–30 years old). In addition, in the elder age group (65–69, 70–74, and ≥ 75 years), Liu et al. [39] also demonstrated a non-significant difference in five-year OS across age range groups. Contrarily, Hutajulu et al. [37] revealed a significant difference in five-year OS between younger and older age groups (<50 vs. ≥ 50 years).

A lower OS in the older age group has resulted from cumulative carcinogenic exposure, somatic mutation, and physiological function deflation. A higher carcinogenic exposure accumulation in older age groups caused the somatic mutation [64]. The deoxyribonucleic acid (DNA) repair imbalance, which also contributed to hypermutation, perpetuated the somatic mutation as

an aging process [65]. In addition, radiation treatment with ionizing radiation that targeted the DNA breaks in cancer cells might be inefficient as there was an imbalance in DNA repair mechanisms in the older age group [66]. On the other hand, cancer chemotherapy agents' effectiveness was also relatively low in elderly patients, as some therapeutic constraints that hindered therapeutic outcomes were applied in the older age group due to lower physiological function and adverse effect minimization [67,68].

The female sex group demonstrated better three-year OS than males in our study, but it was not statistically significant. Some previous studies also indicated similar results to ours, in which females had a better OS, though with various significance levels [36,40,69]. Some independent studies revealed that males had better OS than females, even though not statistically significant [27,39,70]. On the other hand, a more extensive study on gender-specific OS found that females performed better in ten-year OS than males, even in premenopausal and perimenopausal but not postmenopausal patients [71]. Some biological differences between females and males might explain these results, such as hormonal (estrogen, testosterone, and progesterone) differences that affect the physiological processes of metabolism, immunity, and epigenetics in tumor cells [72]. The difference in social constructs also benefited females in terms of having a better OS. Rana et al. revealed that females tended to be diagnosed earlier due to a spillover effect from gynecologic (breast and cervical) cancer awareness on early detection and treatment of non-gynecologic cancer [73]. In addition, females also demonstrated better health-seeking behavior [74].

NPC patients with comorbidities demonstrated a better three-year OS than their counterparts but were not statistically significant. Statistical pitfalls might complicate this result (explained in another section). It also conflicted with some previous studies. Wang et al. [75] found that NPC patients with no comorbidities had a better five-year OS than patients with comorbidities, but this was not statistically significant. Conversely, Huang et al. [76] demonstrated that NPC patients with lower comorbidity scores (ACE-27 score <2) had a significantly better 10-year OS. In addition, Huang et al. [70] revealed that NPC patients with a Charlson Comorbidity Index (CCI) score of 0 had a significantly better 10-year OS than their counterparts (CCI score >0). ACE-27 and CCI share the same comorbidities, such as hypertension, chronic obstructive pulmonary disease (COPD), diabetes, and cardiovascular diseases [21]. A nationally representative cohort study of some cancer patients indicated that the most prevalent comorbidities were hypertension, chronic obstructive pulmonary disease, diabetes, and cardiovascular diseases [77]. These disease-specific comorbidities had intersecting risk

factors and pathomechanisms that shape cancer biology and survival—inflammation. This chronic disease-induced inflammation contributed to cancer pathomechanism (tumor biology and metastasis) and anticancer resistance through complex cellular mechanisms [78]. This complex cellular interaction also impacts functional (performance) status, as NPC patients with comorbidity might have therapeutic constraints to minimize [67,68].

NPC patients with the ECOG performance scale >1 had a better three-year OS than their counterparts, even though it was not statistically significant. This result conflicted with some previous studies and had statistical pitfalls. Alshamsan et al. [79] demonstrated a significantly better four-year OS for NPC patients with better performance status (ECOG scale ≤ 1) than their counterparts (ECOG scale >1). Hutajulu et al. [37] also indicated a significantly better four-year OS for NPC patients with an ECOG scale ≤ 1 than their counterparts (ECOG scale 2 and 3). NPC patients with worse performance status had lower OS as they had more difficulty tolerating rigorous cancer treatments, as nearly all anticancer treatments had the potential for severe side effects [80]. The risks of using specific treatments in patients with poor performance status may significantly outweigh the benefits [81]. Their performance status might gradually decline as cancer progresses in the absence of therapy or cumulative treatment adverse effects [80]. Therapeutic approaches that minimize the side effects of cancer therapy for NPC patients with poor performance status in clinical decision-making might achieve durable clinical benefits from treatment [67,68]. Unfortunately, cancer patients with low-performance status were barely included in clinical trials, resulting in scarce evidence for choosing treatment options for low-performance status patients [68,82]. On the other hand, effective cancer treatment in patients with lower performance status only ameliorated constrained symptoms related to cancer rather than other persistent medical conditions, such as comorbidities [80].

The drop-out patients exhibited worse three-year survival analysis than non-drop-out patients, but not statistically significant. Some previous studies also indicated similar results but with divergent significance levels. Xu et al. [83] and Yao et al. [84] demonstrated that even an interruption in cancer radiotherapy resulted in a significant difference in five-year OS between NPC patients who interrupted and those who did not. NPC patients who dropped out during the treatment would have disease progression as the absence of cancer therapy interrupted cancer progression and development [41,42]. In addition, some identified reasons behind their drop-out related to poor treatment outcomes and adverse effects, insufficient family support, and an alternation to complementary and/or alternative medicine [19]. Furthermore, age (ageism, older age,

geriatric syndrome), mobility, transportation, and healthcare access also contributed to cancer treatment drop-out [85].

This study did not demonstrate any statistically significant results, although some might be consistent with the theoretical basis or previous studies. We identified some statistical issues contributing to the drawbacks: selection, representativeness, small numbers, and censoring bias [86-88]. Selection and representative bias came from the relatively high attrition percentage (67.5%) due to unavailable and inadequate medical records data (**Figure 1**). In addition, accrual time shortages also led to selection bias, as we exclusively included patients newly diagnosed with NPC in 2018 but not in other years due to a pragmatic issue. Combining these two resulted in a small number of samples, which led to a small sample bias; even the actual sample size exceeded the calculated minimum sample size from the previous study. Furthermore, a small sample size inflated the type I error, but we failed to reject the null hypotheses in the study [89].

Most of the samples were right-censored in the study. Censoring impacted a suspiciously drastic fall in step-wise survival function [24]. Small sample size also resulted in higher variance in the small size group proportion, which further amplified the suspiciously drastic fall in step-wise survival function by crossing the survival function line within a group, such as in sex, stage, histological classification, performance status, comorbidity, and therapy drop-out (see **Table 1** and **Figure 3**) [24,33,90]. Consequently, it will inflate the type II error, even though weighted adjustments were applied in the log-rank test [33]. This condition highly influenced our study. Furthermore, the effect of right censoring alone in a nearly balanced small sample size group (e.g., in age at diagnosis and therapy response (see **Table 1** and **Figure 3**)) also led to a suspiciously drastic fall in survival function curves that cross each other within strata [24,33]. These conditions were unlikely to detect a difference; even in this case, the type I error might be inflated [33,89].

Since the statistical power in the log-rank test was dependent on the number of event outcomes (death) rather than the number of subjects, a longer accrual time and longer follow-up might be needed for a retrospective hospital-based medical record survival analysis study to reach a large number of patients [91]. The lack of power in the study led to a small chance of detecting actual effects, which were distorted by random and/or systematic bias [92]. On the other hand, a shorter follow-up, such as in this study, would result in right censoring due to the unobserved event (death) for NPC patients who were still alive at the end of the follow-up time in this study, as we observed a relatively long horizontal line with the tick marks at the tail KM curve and not reaching the median OS threshold for

all epidemiological characteristic stratified survival functions (**Figure 3**). This condition would lead to data immaturity [93]. In addition, this condition was quite common in some studies with pragmatic constraints, such as time and financial constraints [24]. Moreover, relatively long vertical lines were observed in the early or middle of the survival function line as NPC patients were right-censored due to loss of follow-up. We have reached out to confirm the vital status of NPC patients, but most were inaccessible and non-responsive. In addition to the small sample size bias in the study, a small number of NPC patients who were at risk (**Figure 3**) might threaten the precision estimate and compromise generalizability, as representative bias was introduced in the analysis [93].

Another statistical/methodological limitation was the OS estimate, as we did not specify the cause of death of NPC patients as there was no death certificate or autopsy. In addition, we also assume that there was no competing risk, as the KM assumption held in the study [17].

Our study was limited to the Javanese population as our hospital received vertical referrals from districts/cities in Central Java where Javanese lived in Central Java, Yogyakarta, and East Java [16]. This study might capture NPC OS variation between regions and be comparable to similar ethnically homogenous hospital settings, such as Dr. Sardjito General Hospital, Yogyakarta [37].

CONCLUSIONS

We found a satisfactory NPC three-year OS. We also found no statistically significant difference between the NPC patient groups in epidemiological characteristics-stratified three-year OS.

DECLARATIONS

Competing interest

The authors declare no competing interests in this study.

Ethics approval and consent to participate

The Institutional Review Board of the Faculty of Medicine, Universitas Diponegoro/Dr. Kariadi General Hospital (No. 1020/EC/KEPK-RSDK/2022) has approved this study. Informed consent for all patients was obtained upon their first admission to the hospital.

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