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ORIGINAL REPORT

A Health Systems Analysis of Global Head and Neck Cancer Outcomes

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ABSTRACT

Objectives: Head and neck cancer (HNC) remains a major global cause of cancer morbidity and mortality, with disproportionately poor outcomes in low- and middle-income countries. Substantial cross-national disparities suggest an important role for health system strengthening. We evaluated associations between national health system characteristics and global HNC outcomes.

Methods: We conducted a cross-sectional ecological analysis of 185 countries using sex-stratified, age-standardized incidence and mortality estimates from the International Agency for Research on Cancer (IARC) GLOBOCAN 2022 database. The primary outcome was the composite mortality-to-incidence ratio (MIR) for aggregated HNCs, including cancers of the lip and oral cavity, oropharynx, larynx, nasopharynx, hypopharynx, and salivary gland. Eleven national health system indicators capturing health financing, workforce density, service availability, socioeconomic development, and gender equity were evaluated. Univariable linear regressions identified candidate variables using Bonferroni correction ($p < 0.0045$), followed by multivariable modeling with assessment for multicollinearity using variance inflation factors.

Results: All 11 health system indicators were significantly associated with HNC MIR on univariable analysis ($p < 0.001$ for all). In multivariable analysis of 123 countries with complete data, higher Universal Health Coverage (UHC) service coverage index and higher gross domestic product (GDP) per capita were independently associated with lower (improved) HNC MIR (model $R^2 = 0.70$). Findings were consistent in sex-stratified analyses.

Conclusions: Across countries, progress toward universal health coverage and greater national economic capacity was independently associated with improved HNC outcomes. These findings may help to inform efforts at the level of health systems to improve HNC outcomes worldwide.
Level of Evidence: N/A.

1 | Introduction

Head and neck cancers (HNC) collectively represent among the most common cancers globally [1, 2]. HNCs contribute significantly to the total global burden of cancer [2–4]. In 2022 alone, 950,000 new cases and 480,000 deaths for HNCs were recorded [1]. Over the last decades, global age-standardized incidence rates (ASIR) have been increasing [5].

Furthermore, many HNCs disproportionately affect people in low- and middle-income countries (LMICs) despite advances in early detection and treatment [3, 6], reflecting unequal exposure to risk factors driven by regional disparities and socioeconomic determinants [5, 6]. Outcomes are disparate across and within countries, reflecting complex systems level factors including national healthcare resources, cancer policy, financial protection, and access to cancer services [7–11].

With a projected disproportionate rise in ASIR and consistently high age-standardized mortality rates (ASMR) among LMICs over the coming years [5], a greater understanding of health system factors that influence HNC outcomes may inform cancer care planning. We used the Global Cancer Observatory (GLOBOCAN) 2022 estimates of HNC at the country level and health system factors from global agencies to identify the factors that may be associated with HNC outcomes.

2 | Methods

2.1 | Data Sources and Measures

We assembled a cross-national dataset integrating health system indicators from the World Health Organization (WHO), World Bank, the DIrectory of RAdiotherapy Centres (DIRAC), the United Nations Development Programme (UNDP), and cancer burden estimates from the International Agency for Research on Cancer (IARC); we sought to construct a comprehensive set of national health system indicators spanning health financing, workforce capacity, service availability, socioeconomic development, and gender equity.

Metrics included health expenditure as a percentage of gross domestic product (GDP); physicians, nurses/midwives, and surgical workforce density per 1000 population; GDP per capita; progress toward universal health coverage as measured by the Universal Health Coverage (UHC) service coverage index; availability of pathology services; radiotherapy capacity measured as radiotherapy centers per 1000 population; the Human Development Index (HDI); the Gender Inequality Index; and out-of-pocket expenditure as a percentage of current health expenditure (listed in Table 1). The analytic dataset was frozen on November 27, 2024.

TABLE 1 | Univariable analyses associating health system variables with cancer MIR for both sexes.[a]

Health system measure	*N* complete	*β* coefficient	95% CI (lower bound)	95% CI (upper bound)	*p*
Health spending as % of GDP	171	−0.02062	−0.02831	−0.01293	< 0.001
Physicians per 1000 population	167	−0.05888	−0.06998	−0.04779	< 0.001
Nurses/midwives per 1000 population	166	−0.02729	−0.03164	−0.02294	< 0.001
Surgical workforce per 1000 population	144	−0.00234	−0.00294	−0.00173	< 0.001
UHC index	175	−0.00766	−0.00868	−0.00663	< 0.001
Pathology services (yes vs. no)	174	−0.17943	−0.2378	−0.12105	< 0.001
Human development index	177	−0.85424	−0.95262	−0.75586	< 0.001
RT centers per 1000 population	185	−79.5727	−96.4761	−62.6693	< 0.001
GDP per capita	185	−5.28E−06	−6.12E−06	−4.43E−06	< 0.001
Gender inequality index	165	0.610201	0.519817	0.700584	< 0.001
Out of pocket (%)	171	0.003139	0.0018	0.004477	< 0.001

[a]World Bank health system covariates included: health expenditure as a percent of gross domestic product (GDP), physicians per 1000 population, nurses/midwives per 1000 population, surgical workforce per 1000 population, out-of-pocket expenditure as a share of current health expenditure, and GDP per capita. WHO variables included Universal Health Coverage Service Coverage Index (higher scores denote greater coverage) and national availability of pathology services. UNDP variables included Human Development Index (HDI) and Gender Inequality Index (GII; lower values indicate greater gender equity). DIRAC provided counts of radiotherapy (RT) centers; using 2023 World Bank population figures, we calculated centers per 1000 population.

For 185 countries, sex-stratified age-standardized cancer incidence and mortality rates were obtained from the International Agency for Research on Cancer (IARC) GLOBOCAN 2022 database, which synthesizes the best available national data from population-based cancer registries, vital registration systems, and modeled estimates where empirical data are incomplete [1]. Rates were age-standardized to the Segi–Doll world standard population to facilitate cross-national comparisons [1].

The primary outcome was the composite mortality-to-incidence ratio (MIR) for aggregated HNCs, defined as cancers of the lip and oral cavity, oropharynx, larynx, nasopharynx, hypopharynx, and salivary gland. Despite heterogeneity in risk factors and treatment paradigms, these diseases were aggregated given the common need for multimodality treatment for these conditions in the primary analysis.

Furthermore, MIR was selected as the primary outcome because it provides a pragmatic, population-level proxy for cancer survival in settings where reliable stage-specific survival data are not uniformly available [1]. MIR allows comparison across countries with markedly different incidence patterns by relating mortality to underlying disease burden. This metric has been widely used in global oncology research across multiple cancer types to evaluate disparities in cancer outcomes and health system performance [12–15]. Given the ecological, cross-national scope of this study and the lack of standardized survival datasets spanning 185 countries, MIR represents a feasible and internationally comparable measure of relative cancer outcomes.

2.2 | Statistical Analysis

Univariable linear regressions evaluated the relationship between HNC MIR and each covariate. Variables surpassing a Bonferroni-corrected threshold ($p<0.0045$ for 11 tests) were carried forward to multivariable modeling.

To mitigate concerns regarding multicollinearity among health system indicators, many of which are conceptually correlated, we conducted variance inflation factor (VIF) analysis prior to final model specification. Variables demonstrating substantial collinearity (VIF > 10) were excluded to preserve model stability and improve interpretability of regression coefficients. This approach reduces inflation of standard errors, limits spurious associations arising from correlated predictors, and enhances confidence that independent associations identified in the multivariable model reflect statistically stable relationships. Nonetheless, residual correlation between structural health system variables is unavoidable in global ecological analyses and must interpret these findings accordingly.

In the multivariable model, two-sided $\alpha=0.05$ defined significance, and goodness of fit was summarized by R^2.

2.3 | Site-Specific Sub-Analysis

To assess whether the association between UHC and MIR differed by anatomical site, we performed a post hoc site-specific analysis for hypopharynx, larynx, lip/oral cavity, nasopharynx, oropharynx, and salivary gland cancers. To mitigate multiple hypothesis testing, we limited this additional analysis to the UHC index only. First, we evaluated the association between UHC and site-specific MIR using univariable linear regression. Second, we incorporated UHC into multivariable models using the same covariates as in the primary analysis (health spending as percent of GDP, physician density, nursing/midwife density, surgical workforce density, pathology availability, radiotherapy centers per population, GDP per capita, Gender Inequality Index, and out-of-pocket expenditure), with $\alpha=0.05$ defining significance.

This analysis used only publicly available, aggregate country-level data and was therefore not considered human subjects research; institutional review board oversight was not required.

3 | Results

Data from 185 countries were included based on the availability of cancer incidence and mortality estimates from the IARC. The completeness of health system indicators varied, ranging from 144 countries (77.8%) for surgical workforce data to 185 countries (100%) for GDP per capita. In univariable analyses, all 11 health system metrics spanning health system resources, workforce capacity, and UHC coverage were significantly associated with the cancer MIR ($p<0.001$ for all; Table 1).

Accordingly, the initial multivariable model included all 11 health system metrics; 123 countries had complete data, yielding an R^2 of 0.7273. VIF analysis indicated collinearity for the HDI (VIF > 10). The model was therefore re-estimated excluding HDI. In this final model, VIF values for all remaining metrics were < 10.

The final model ($N=123$ countries) with 10 metrics had an R^2 of 0.7021 (Table 2). VIF for all metrics was < 10. Therefore, the following variables were associated with lower (improved) MIR for HNCs: (1) UHC index and (2) GDP per capita. MIR is plotted individually against these four metrics in Figure 1. On analysis stratified by sex, UHC index and GDP per capita were similarly independently associated with improved MIR for HNCs.

3.1 | Site-Specific Sub-Analysis

On univariable analysis, greater UHC index was significantly associated with lower MIR for all anatomical sites examined: hypopharynx (β −0.0063, $p<0.001$), larynx (β −0.0070, $p<0.001$), lip/oral cavity (β −0.0083, $p<0.001$), nasopharynx (β −0.0077, $p<0.001$), oropharynx (β −0.0051, $p<0.001$), and salivary gland cancers (β −0.0099, $p<0.001$).

In multivariable models including the same health system covariates as the primary analysis, greater UHC index remained independently associated with improved (lower) MIR for hypopharynx (β −0.0122, $p<0.001$), lip/oral cavity (β −0.0051, $p=0.001$), nasopharynx (β −0.0070, $p<0.001$), oropharynx (β −0.0055, $p=0.016$), and salivary gland cancers (β −0.0120, $p<0.001$). The association between UHC and MIR was not

TABLE 2 | Multivariable analyses associating health system variables with cancer MIR after removing variables with significant multicollinearity.

Health system measure	β coefficient	95% CI (lower bound)	95% CI (upper bound)	p
Health spending as % of GDP	−0.0013763	−0.0084169	0.0056643	0.699
Physicians per 1000 population	0.0057128	−0.0161321	0.0275578	0.605
Nurses/midwives per 1000 population	−0.0046893	−0.0129004	0.0035218	0.26
Surgical workforce per 1000 population	−0.0000111	−0.0009147	0.0008925	0.981
UHC index	−0.0050472	−0.0073959	−0.0026985	<0.001
Pathology services (yes vs. no)	−0.030193	−0.0833609	0.0229749	0.263
RT centers per 1000 population	−1.193339	−21.21981	18.83313	0.906
GDP per capita	−2.22E-06	−3.55E-06	−8.94E-07	0.001
Gender inequality index	−0.0350507	−0.2775898	0.2074884	0.775
Out of pocket (%)	0.0001174	−0.0010549	0.0012898	0.843

Note: This model had R^2 of 0.7021.

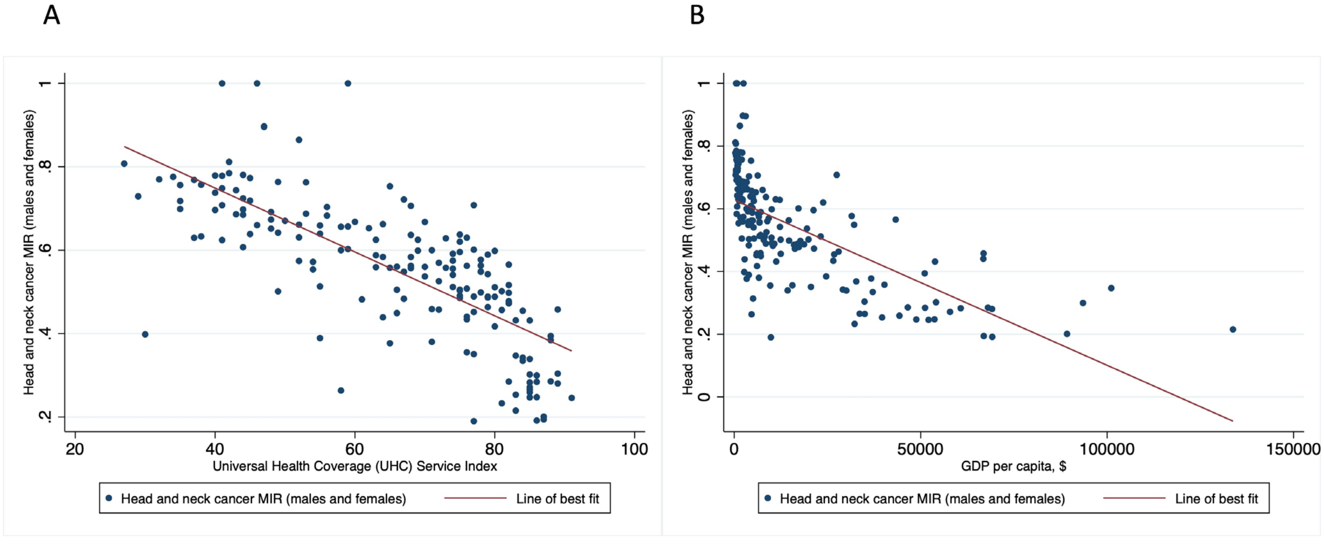

FIGURE 1 | Head and neck cancer mortality to incidence ratio (MIR) in association with universal health coverage (UHC) service index (A) and gross domestic product (GDP) per capita (B).

statistically significant for laryngeal cancer in the multivariable model (β −0.0013, p = 0.407).

4 | Discussion

The increasing burden of HNCs globally may reflect inequities in cancer care that translate to systemic gaps in prevention, early detection, and treatment, especially in resource-constrained settings [6, 16]. Through our global comparative analysis, we explored how global health indicators may be associated with MIRs for HNCs in order to offer insight into drivers of outcome disparities.

Our study found that on univariable analysis, all 11 health system metrics were significantly associated with HNC MIR. Furthermore, the association between greater UHC and improved outcomes is broadly consistent across HNC subsites, with the exception of laryngeal cancer in adjusted analyses. These findings highlight how these health system determinants may serve as actionable targets for future policy interventions to reduce HNC burden [17, 18].

Given the interrelated nature of these indicators, the independent association of UHC may reflect the importance of healthcare financing and protection from financial toxicity [19]. UHC encompasses not only access to essential health services but also financial risk protection across prevention, diagnosis, treatment, and survivorship, underscoring its central role in mitigating financial toxicity and improving cancer outcomes [8, 20, 21].

Additionally, as many HNCs arise from modifiable exposure to risk factors such as tobacco, betel nut use, alcohol, HPV infections, the expansion of UHC as a means to facilitate behavior and exposure modifications especially in LMICs may reduce the disproportionate burden of HNC [19, 22]. UHC strategies should be context-specific, accounting for regional variations in HNC risk and health resources [23].

Furthermore, the independent association of GDP per capita on multivariable analysis underscores the role of macroeconomic capacity as a structural determinant of population-level cancer outcomes [7, 15, 24]. Higher national income may reflect greater fiscal space to invest in health infrastructure, workforce development, diagnostic capacity, treatment availability, and social protection mechanisms that reduce financial barriers to care [20, 25]. Relatedly, economic development may influence cancer survival not only directly through health system spending, but also indirectly through broader investments in education [26], infrastructure, and institutional stability [7, 21] that support effective cancer control.

Importantly, these findings should not be interpreted to suggest that only UHC and national wealth matter for HNC outcomes [15]. Rather, the attenuation of other health system variables in multivariable models likely reflects the high degree of interrelatedness among health system components, whereby financing, workforce capacity, infrastructure, and service availability co-evolve within countries. The fact that multiple indicators, including health spending, workforce density [27], pathology availability, radiotherapy capacity [28], and financial protection [25, 29, 30], were each significantly associated with HNC MIR on univariable analysis underscores that health system strengthening is inherently multidimensional. In this context, UHC and GDP per capita may function as integrative markers of broader system capacity rather than isolated drivers, reinforcing the need for comprehensive health system investment rather than singular policy levers [7, 9, 31].

These findings should be interpreted in the context of several important limitations. First, this ecological analysis relied on publicly available, country-level data, which are subject to variation in cancer registry coverage, data quality, reporting accuracy, and completeness across countries, particularly in low- and middle-income settings where cancer surveillance infrastructure may be limited [1, 2]. Although GLOBOCAN applies standardized and validated estimation methods to address data gaps, residual uncertainty and misclassification may persist and could influence estimated incidence, mortality, and derived MIRs [1, 2, 4].

Furthermore, limitations of MIR should be acknowledged. MIR is an ecological proxy for survival and does not directly measure patient-level outcomes. MIR may be influenced by differences in cancer registration completeness, diagnostic intensity, or death certification accuracy across countries. Furthermore, MIR does not fully account for stage distribution at diagnosis, variations in tumor biology (e.g., HPV-associated disease), or treatment heterogeneity. Accordingly, MIR should be interpreted as a population-level approximation of cancer outcomes rather than a direct measure of survival.

Although we conducted VIF analysis to mitigate multicollinearity among correlated health system indicators and excluded variables with substantial collinearity to improve model stability, many structural health system metrics (e.g., GDP per capita, workforce density, and UHC index) are inherently interrelated. As such, complete statistical separation of these constructs is not possible in ecological cross-national analyses.

Although we specified linear regression models and evaluated model fit metrics (including R^2) to assess explanatory performance, we also acknowledge that linearity assumptions may not fully capture potentially nonlinear or threshold relationships between health system indicators and MIR.

In addition, the use of aggregated national metrics precludes adjustment for within-country heterogeneity in access to care, socioeconomic status, and health system capacity, as well as individual-level risk factors such as tobacco and alcohol use, HPV and/or EBV status, comorbidities, and stage at diagnosis, all of which are known to influence HNC outcomes [10, 16]. Further work must also explore disparities in access to survivorship and supportive care [32]. Lastly, the cross-sectional design limits causal inference and does not capture temporal changes in health system investments or cancer outcomes.

5 | Conclusion

Our global cross-national analysis demonstrates that universal health coverage and national economic capacity are consistently associated with improved HNC mortality-to-incidence ratios, underscoring the role of health system strength in cancer outcomes. These findings highlight how investments in healthcare access, financial protection, and resource availability may be associated with narrowing persistent global disparities, particularly in low- and middle-income countries. These findings may help to inform efforts at the level of health systems to improve HNC outcomes worldwide.

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Disclosure

The funders did not influence the following aspects of the manuscript: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of Interest

N.Y.L. serves on the advisory boards (consultant) with Merck, Merck Serono, J and J, Nanobiotix, Galera, LEO SAB, and GSK. N.Y.L. holds stock options with LEO SAB. P.I. received research grants from Incyte (to the institution) and has participated in the Advisory Board of AstraZeneca, Novocure, Johnson and Johnson, BioConvergent Health, Pfizer, and NGM Biosciences. E.C.D. declares no competing interests. All other authors report no relevant COI.

Data Availability Statement

Data are publicly available from the World Health Organization, the World Bank, and the Global Cancer Observatory.

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