COMMENTARY

Insurance-based Disparities in Gastro-Entero-Pancreatic Neuroendocrine Tumor Patients

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Abbreviations: Gastero-entero-pancreatic neuroendocrine tumors (GEP-NETs), coronavirus disease 2019 (SARS-CoV-2), US-Neuroendocrine Tumor Study group (US-NETSG)
Abstract: In the United States, uninsurance remains a major barrier in accessing health care for many citizens and residents. Studies have shown that uninsured patients with many cancers and chronic diseases have worse survival than insured patients. A recent study similarly showed that uninsured patients with gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) have significantly shortened survival. While GEP-NETs are indolent tumors with generally favorable prognosis, comprehensive care involves years of surveillance, imaging, and treatment following resection, all of which carry a large financial burden. In this commentary, we expand on these findings as they relate to insurance-based disparities as well as management and policy implications.

Key words: Insurance, cancer, disparity, health, survival, SARS-CoV-2.
Although the United States (U.S.) is a leader in biomedical research with early integration of cutting-edge diagnostic and therapeutic approaches, it is evident that a substantial proportion of Americans are unable to enjoy the benefits of such advances. As the U.S. continues to rely on a market-based health care system with the majority of individuals acquiring health insurance through their employers, as of 2019, 27.5 million people (8.5%) remain uninsured and are thus unable to access basic medical care.\(^1\) In the context of the coronavirus disease 2019 (SARS-CoV-2) pandemic, more than six million Americans have lost health insurance they had previously had through their employer. After taking into account spouses and children, the number of those affected has surpassed 12 million with millions more at risk of losing coverage as severance packages and enrollments near their limits.\(^3\)\(^-\)\(^5\)

Concurrently, the complexity and cost of health care in the U.S. continue to rise\(^6\) exaggerating barriers to care for the uninsured. In cancer care specifically, advances in imaging and treatments (i.e., targeted therapies and immunotherapy) have led to highly specialized and multi-disciplinary treatment approaches and a resultant increase in complexity of navigating care and decrease in affordability\(^6\). Consequently, many U.S. cancer patients encounter financial hardship following their cancer diagnosis\(^7\)\(^-\)\(^8\). These financial challenges are particularly significant among uninsured and underinsured patients\(^7\) who are often forced to choose between receiving comprehensive care or financial ruin.

Previous studies have demonstrated shortened survival in uninsured cancer patients in the U.S. compared with their insured counterparts\(^9\)\(^-\)\(^16\) and that low-income Americans with cancer have worse survival than low-income cancer patients in countries with universal health care\(^17\)\(^-\)\(^18\). However, the relationship between insurance status and survival in gastro-entero-neuroendocrine tumors (GEP-NETs) in the U.S. has remained unexamined until recently. GEP-NETs are of particular interest considering their unique clinical course. While many
gastrointestinal cancers are highly aggressive with rapid progression and relatively poor prognosis despite maximal therapy, GEP-NETs typically demonstrate an indolent course and favorable prognosis.\textsuperscript{19} Although poor outcomes are associated with delayed presentation and unresectable disease,\textsuperscript{19} many GEP-NET patients ultimately survive for many years after diagnosis, undergoing multiple operations and re-operations as well as long term treatment, suppressive therapy, and surveillance. Such a prolonged and arduous clinical course may contribute to the financial burden of the diagnosis. Additionally, the natural history and treatment course of GEP-NETs mimics that of other non-malignant chronic diseases (including inflammatory bowel disease, diabetes mellitus, chronic renal failure, and Alzheimer’s disease) more closely than it does other gastrointestinal malignancies.

In a retrospective cohort study published recently using the US-Neuroendocrine Tumor Study group (US-NETSG) database, Marincola Smith and colleagues examined insurance-based disparities among 1,425 patients aged 18 to 65 years old who underwent surgical resection of GEP-NETs at eight large academic medical centers across the U.S. from 2000 to 2016\textsuperscript{20}. They demonstrated that in this large cohort, uninsured was an independent risk factor for worse overall survival following primary resection of a GEP-NET after controlling for T/M stage, tumor grade, ASA class, and inferred income status (Hazard ratio [HR] 2.69, 95% confidence interval 1.32-5.48, p<0.01). While insured patients were found to have 1-, 5-, and 10-year survivals of 96%, 88%, and 74%, uninsured patients’ 1-, 5-, and 10-year survivals were lower at 88%, 72%, and 44% (p<0.01), respectively.

Importantly, GEP-NETs are notoriously difficult to diagnose and often present with vague symptoms requiring multiple doctor’s visits over many months or years before a definitive diagnosis is reached and management initiated\textsuperscript{21}. Therefore, it is logical to suggest that the survival disparity observed may be attributable to delays in diagnosis for uninsured patients who
are likely to face challenges in accessing primary care visits and diagnostic tests. However, in this study, insured and uninsured patients were found to have similar pre-operative tumor size as well as similar TNM stage and tumor differentiation on final pathologic specimen, suggesting the groups had similar disease characteristics at the time of resection. These findings suggest there may be other factors related to pre-, intra-, or post-operative management, aside from simply delayed diagnosis, influencing mortality.

Although overall rates of neoadjuvant and adjuvant chemotherapy were similar between insured and uninsured patients, uninsured patients were significantly less likely than insured patients to receive post-operative somatostatin analogue therapies (2% vs. 10%, p=0.03). Somatostatin analogues are known to decrease morbidity and mortality by preventing tumor progression/recurrence and controlling symptoms of hormone hypersecretion in GEP-NETs. However, these therapies can cost over $6000/month, which may be cost-prohibitive for some uninsured patients and could partially explain the disparity in use between insurance groups. While the disparity in post-operative somatostatin analogue therapy use and the known costs of the therapy suggest that difficulty acquiring appropriate adjuvant therapies may be contributing to the shortened survival observed among uninsured patients with GEP-NETs, importantly, it is impossible to prove the cause of this disparity between groups given the lack of insight into the patient and physician’s shared decision-making process. This inherent limitation of retrospective cohort studies limits the authors’ ability to assign causation to the observed survival disparity in uninsured patients with GEP-NETs generally and also to the disparity in post-operative somatostatin analogue therapy use; further targeted and prospective investigation would be needed to definitively prove causation.

Another important potential confounder is the relationship between insurance status and income level. Certainly, uninsured patients are by and large more likely to have lower incomes
than their insured counterparts. However, this is not universally true, given that some self-employed individuals may have relatively high incomes without employer-based health insurance. On the other hand, low-income individuals, including those living below the poverty line, may have government-based health insurance (Medicaid). Low-income individuals, whether uninsured or government-insured, may face challenges related to socioeconomic status that are independent of health insurance coverage, including family support structure, access to secure housing, healthy food, transportation, and tertiary cancer centers. These social determinants of health seem likely to impinge on patient outcomes within and outside the context of a complex cancer diagnosis, and it is important to assess income level as a confounding variable when examining the effects of insurance status on survival.

Although income level could not be directly assessed, Marincola Smith and colleagues attempted to examine this relationship in three ways. First, they approximated each patient’s income level, according to the Center for Medicare and Medicaid Services Database, which assigned each patient a designation of “high” or “low” income based on their home ZIP code. Using this method, income level was found to be similar in insured (including Medicaid and private insurance) versus uninsured patients (47% versus 44% living in low-income ZIP code, p=0.36). Second, when controlling for inferred income level on multivariable analysis, insurance status was independently predictive of shortened survival following resection for GEP-NETs. Third, recognizing insured patients likely demonstrate heterogeneity in income level, the insured group was split into privately insured (primarily high-income) and Medicaid insured (primarily low-income). These two insured subgroups demonstrated nearly identical survival curves, and both insured subgroups had significantly improved survival compared with uninsured patients. All of this together suggests that it is health insurance itself, or more specifically the access to
medical care afforded by having health insurance, that contributes most significantly to the observed survival disparity, more so than the socioeconomic confounders discussed above.

Certainly, many of these socioeconomic factors (including education, health literacy, social network) are colinear with uninsurance and further analysis to tease out the contributions and confounding impact of each factor would be helpful. Additionally, the prevalence and management of particular comorbidities among the insured and uninsured patients would be of particular interest. Although the authors compare and control for ASA class in their analysis, they do not assess individual comorbidities (including diabetes mellitus, hypertension, obesity) each of which may affect patient outcomes and may be more prevalent and/or inadequately managed among uninsured patients.

Furthermore, it is important to note that, although Marincola and colleagues’ study effectively demonstrates survival disparities in patients who underwent primary resection for GEP-NETs, the study likely underestimates the true insurance-based disparities among GEP-NET patients considering many uninsured patients have difficulty accessing the health care system and obtaining elective operations. It is highly likely many uninsured patients with GEP-NETs never make it to primary resection and therefore were not included in the study cohort. Because the primary treatment (and the only chance at cure) for GEP-NETs is complete surgical resection, patients unable to access surgical resection are likely to have a poor prognosis.\textsuperscript{19} While 4.4\% of the study cohort was uninsured, the average annual uninsurance rate in the U.S. over the study period was about 16\% among the non-elderly U.S. population,\textsuperscript{27,28} suggesting uninsured patients are under-represented in the US-NETSG database and possibly among the general population of patients who undergo primary surgical resection for GEP-NETs in the U.S. For these reasons, it is highly plausible the survival disparity between insured and uninsured patients following GEP-NET diagnosis is even wider than that discovered in the study published by Marincola Smith and
colleagues. While uninsured patients are generally likely to experience more barriers to diagnosis and treatment, the current SARS-CoV-2 pandemic has imposed an unprecedented burden on the U.S. health care system and such a disruption has limited access to care for both insured and uninsured patients.

Furthermore, the chronicity of GEP-NET management makes these cases uniquely onerous financially relative to more common gastrointestinal malignancies (such as colon or pancreatic cancer), with costs often accruing months to years after diagnosis. Aside from the direct medical costs attributable to GEP-NET diagnosis and treatment, the need for highly specialized care, frequent office visits, and the burden of tumor-, surgical-, and therapy-related symptoms and complications have been shown to impinge negatively on employability, which in and of itself could affect mental, physical, and financial health as well as health insurance coverage. It is thus not surprising uninsured patients paying for care out-of-pocket may forego some expensive and burdensome treatments or defer recommended surveillance either by choice or by necessity.

As was observed in the US-NETSG cohort, national rates of uninsurance declined following implementation of the Affordable Care Act in 2010. Across many large studies, the increased proportion of insured Americans was associated with decreased overall mortality, providing evidence that insurance coverage in the U.S. saves and extends lives. This is consistent with an Institute of Medicine report, which identified uninsurance as being associated with an overall increased risk of all-cause mortality (HR 1.03–1.29).

These findings beg an important question as to whether the disparities observed in this cohort, as well as others, could be relieved by ad hoc cancer-specific financial assistance programs or if, conversely, such survival disparities stem from factors rooted in extended periods of uninsurance. In the latter case, access to cancer care without general health insurance
coverage may be, in fact, “too little too late.” Already, roughly one in 20 Americans have lost their insurance since the beginning of the pandemic in spring 2020, further limiting access to care for a large and increasing segment of the U.S. population. Furthermore, studies have shown these historic unemployment rates have disproportionality affected low-income and marginalized minority groups further exacerbating existing health care disparities among such populations. 2-5,37

Aside from the direct strain on the health care system experienced in the face of resource shortages (including personnel, personal protective equipment), the current challenges have further exposed the vulnerability of the American people to economic downturns and just how threadbare employer-based health insurance is. The need to delink coverage from specific employment has likely never been greater. Should another recession occur, even withstanding a global pandemic, insurance-based disparities will once again parallel unemployment.

In 2020, roughly 1.8 million people will be diagnosed with cancer in the U.S., and it was estimated that approximately 150,000 of them would be uninsured under current policy. However, due to the wide-ranging global ramifications of the SARS-CoV-2 pandemic, it is estimated that the number of uninsured patients diagnosed with cancer in 2020 may double (in view of the fact that up to 25 million Americans could lose their employer-sponsored health coverage due to unemployment39). Greater understanding of the factors that create cancer- and health-related inequalities can help researchers, clinicians, and policymakers develop strategies and interventions to mitigate these disparities and/or justify the continuation or expansion of current government- and private-based assistance programs. In the end, promoting health equity may be the most expedient way to improve outcomes for some individuals diagnosed with cancer.
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