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## Third Leading Cause of Death Revisited

Written by
Skeptical Scalpel

Ever since the publication of the infamous 2016 *BMJ* opinion piece by Makary claiming medical error should be considered the third leading cause of death in the US, the debate on the true incidence of deaths caused by medical error has been raging. Many, including me, felt the Makary estimate of 251,000 deaths per year from medical error was grossly inflated. For example, Makary extrapolated the number of deaths from three outdated studies with a total of just 35 deaths, and medical error was not well-defined.

A new paper in *BMJ Open Access* by investigators from the UK looked at 70 studies involving 337,025 patients mostly treated in general hospitals. Of that total, 47,148 suffered harm, with 25,977 (55%) of harms judged as preventable.

The authors concluded, "The pooled prevalence for preventable patient harm was 6% (95% confidence interval 5% to 7%). A pooled proportion of 12% (9% to 15%) of preventable patient harm was severe or led to death." I'll do the math; 12% of 6% is 0.72% or just over 2,400 preventable severe harms and deaths.

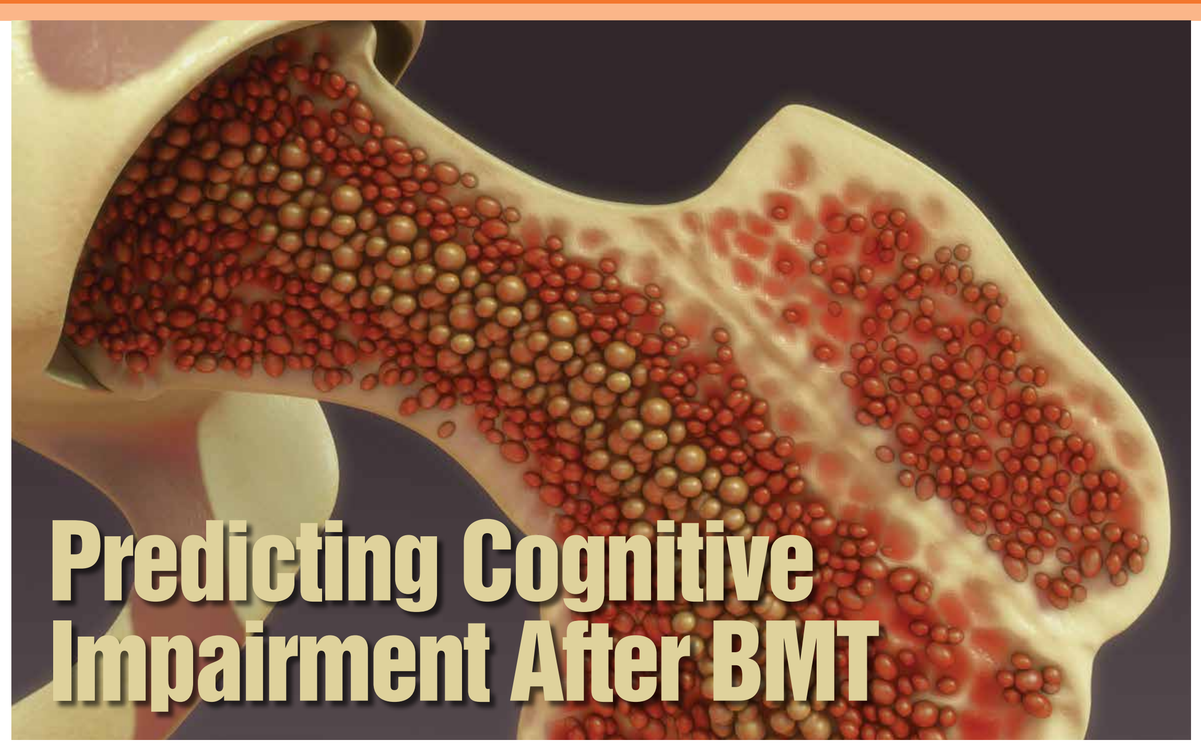
A recent literature review on the website Healthy Debate Canada cited three papers estimating that incidence of preventable deaths due to medical error ranged from less than 1% to 5.2% and said, "This would correspond to 15,000-35,000 deaths per year in the US, an order of magnitude lower than the *BMJ* estimate."

Even one preventable death is too many. However, inflated figures like 251,000 deaths or even 440,000, as a 2013 paper claimed, undermine public confidence in medical care.

Some examples. The Canadian authors said calling medical error "the third leading cause of death" in the US enabled supporters of the NRA to say doctors are more harmful than guns. Naturopaths and alternative news sites warned about the dangers of our health system.

From *Healthy Debate:* "In-hospital deaths from medical error are a small subset of all medical errors, and non-fatal errors cause considerable harm to patients. Considering that most healthcare occurs in the ambulatory setting, there is an even larger potential for error to cause harm outside of hospitals." Focusing too much on in-hospital deaths from error may direct attention away from other areas of quality improvement.

Medical error is not the third leading cause of death in the US. Will people stop saying it is? I doubt it.



# Predicting Cognitive Impairment After BMT

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Previous research indicates that patients undergoing blood or marrow transplantation (BMT) are exposed to potentially neurotoxic treatment. "In a previous study, my colleagues and I found that cognitive impairment is prevalent in patients who had hematologic malignancies and were treated with BMT, up to 3 years after BMT, and those with cognitive impairment were less likely to return to work," explains Smita Bhatia, MD, MPH. With significant interindividual variability in risk for cognitive impairment in this patient population, suggesting a role for genetic susceptibility, Dr. Bhatia and colleagues tested the hypothesis that individual single nucleotide polymorphisms (SNPs) and gene-level variants are associated with cognitive impairment in patients with hematologic malignancies treated with BMT and that inclusion of these SNPs improves risk prediction beyond that offered by clinical and demographic characteristics.

### Considering Genes

For a study published in the *Journal of Clinical Oncology,* Dr. Bhatia and colleagues performed neuropsychological testing on patients prior to treatment with BMT through 3 years after. "Our team hypothesized that chemotherapy and/or radiation induce oxidative stress, resulting in DNA damage and telomere shortening, which could result in neurodegeneration and present as cognitive impairment," adds Dr. Bhatia. The researchers developed a list of biologically plausible SNPs to determine susceptibility. Germline DNA was collected before BMT treatment and genotyped. The team genotyped 68 SNPs identified during the discovery phase and then used tested machine-learning techniques to identify gene markers and develop risk prediction models. The complex analyses were led by Noha Sharafeldin, MD, MSc, PhD.

### The Results

Older age (odds ratio [OR], 4.6), male sex (OR, 3.3), and lower cognitive reserve (OR, 4.6) were associated with the highest risk of cognitive impairment (Table). Dr. Bhatia highlights that patients who received total body irradiation were also at an increased risk when compared with those who did not. Additionally, cognitive impairment following BMT was associated with five SNPs on DNA repair genes (rs13006837, rs293796, rs12534423, rs4725015, and rs7087131), one SNP on the BBB gene (rs10808071), and one SNP on the telomere homeostasis gene (rs1713436), indicating associations of SNPs in DNA repair genes with processing speed and working memory.

"Our study provides useful insights regarding the utility of collecting genetic data in clinical practice to predict post-BMT cognitive impairment," emphasizes Dr. Bhatia. "The combination of genetics, demographics, and clinical make-up can identify BMT recipients at highest risk for cognitive impairment. We can use this information in the future to work closely with BMT recipients at highest risk for cognitive impairment in order to institute cognitive remediation."

Upon further analysis, the team determined the median time between patients receiving BMT treatment and developing cognitive impairment to be 2 years (interquartile range, 1 to 7 years). No demographic or clinical characteristics were independently associated with learning or memory severity. Because of previous reports of fatigue being associated with cognitive decline in patients treated with allogeneic BMT, the team included fatigue as a variable when predicting risk of cognitive impairment. However, they did not find that fatigue was independently associated with cognitive impairment.

### Continuing Research

"Our results suggest that incorporating identified genetic factors significantly enhanced the risk prediction of cognitive impairment and improved the accuracy, as assessed by the C-statistic," notes Dr. Bhatia. "This study represents the first step toward identification of BMT survivors at high risk for cognitive impairment, informing personalized management of cognitive outcomes in patients undergoing BMT. In the future, we would like to develop a diagnostic assay that would be incorporated into a risk prediction tool, which would create a 'personal risk score' for cognitive impairment. Patients at high risk also could benefit from specific interventions to improve cognition."

**Table Characteristics Associated With Post-BMT Cognitive Impairment**

| Characteristic | Odds Ratio | *P* |
|---|---|---|
| BMT type | | .44 |
| Autologous | Ref | |
| Allogeneic | 0.76 | |
| Age, years | | **.002** |
| < 50 | Ref | |
| ≥ 50 | 4.61 | |
| TBI | | .021 |
| No | Ref | |
| Yes | **3.43** | |
| TBI interaction, age, years | | **.024** |
| ≥ 50 | Ref | |
| < 50 | **4.72** | |
| Sex | | **.002** |
| Female | Ref | |
| Male | **3.26** | |
| Race | | .27 |
| Non-Hispanic white | Ref | |
| Other | 1.57 | |
| Education | | .29 |
| ≥ College graduate | Ref | |
| < College graduate | 1.42 | |
| Annual household income, $ | | |
| < 50,000 | Ref | .87 |
| 50,000-100,000 | 0.94 | .06 |
| > 100,000 | 0.37 | |
| Cognitive reserve (IQ) | | **< .0001** |
| High | Ref | |
| Low | **4.60** | |
| Fatigue | | .77 |
| Low | Ref | |
| High | 1.05 | |
| Relapse risk | | .62 |
| High | Ref | |
| Standard | 1.20 | |

Note: Bold type indicates $P < .05$.
Abbreviations: BMT, blood or marrow transplantation; IQ, intelligence quotient; TBI, total body irradiation.
**Source:** Adapted from: Sharafeldin N, et al. J *Clin Oncol.* 2020;38(12):1312-1321.

## Medical Economics®

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### Why We Need a One-to-Many Telehealth Model of Care

*This article was originally published in Medical Economics and is written by Jon Bloom, MD.*

One thing the COVID-19 pandemic has made clear is that telemedicine is a public health necessity. However, real-time, or synchronous, telemedicine isn't sustainable or scalable. We're already seeing synchronous telemedicine practiced on a small scale put a strain on our healthcare system during COVID-19.

For telemedicine to work at scale, it must also have a one-to-many component. In this model, data can be remotely gathered and consistently monitored over time and then used for timely and targeted communication between patients and providers. This allows care to scale from one-to-one to one-to-many.

Fortunately, a model already exists for how we can use asynchronous, one-to-many remote monitoring at scale for even the hardest-to-reach patients. The health system overseen by the VA is now successfully using asynchronous telehealth right now to ensure patients who cannot or should not visit a VA facility are still able to get the frequent care they need from a distance.

One such example is the effort to remotely monitor veterans at risk for diabetic amputations. Veterans place their feet on the Podimetrics SmartMat for just 20 seconds a day in their home, and the temperature data captured is automatically sent to a care management team to monitor. When early signs of issues are detected, patients and providers are notified so clinical action can be taken quickly, helping to prevent more serious complications.

Such large-scale preventive care could not be achieved through synchronous, one-to-one telemedicine. There simply are not enough doctors available to check in with every patient for even 1 minute every day. However, remote asynchronous systems can gather data over time to help prioritize synchronous telemedicine, ensuring patients receive the care they need when it matters most.

A key takeaway of the current pandemic has been the importance of telehealth; however, for it to be sustainable, we need a combination of synchronous and asynchronous patient monitoring tools that allow for targeted communication. We should expect more healthcare providers to incorporate this kind of model to offer access at scale and save lives.

*To read the unabridged version, visit www.medicaleconomics.com.*

## Long-Term NLPHL Follow-up

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Data indicate that nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity accounting for approximately 5% of all Hodgkin lymphoma (HL) cases. The incidence is roughly 0.1-0.2 cases per 100,000 people per year. NLPHL is characterized by a consistent expression of CD20 on the malignant lymphocyte-predominant cells and a rather indolent clinical course. At present, there is no accepted standard of care for the first-line treatment of NLPHL.

To shed more light on the long-term outcomes of patients with NLPHL who were initially treated with stage-adapted HL-directed approaches, we and our colleagues performed a subgroup analysis of nine consecutive randomized phase III trials conducted between 1993 and 2008. For our report published in the *Journal of Clinical Oncology,* 471 patients with NLPHL were taken into account. Treatment consisted of ABVD-based chemotherapy [doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine] followed by consolidation radiotherapy for early and intermediate stages and different BEACOPP [bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone] variants optionally followed by consolidation radiotherapy of larger residual lymphoma for advanced stages. Anti-CD20 antibodies were not given.

At 10 years, the progression-free survival and overall survival estimates were 75.5% and 92.1%, respectively. Thus, outcomes were comparable with those obtained from patients with classical HL. Risk factors associated with impaired outcomes were age 45 and older and liver, bone marrow, and splenic involvement. Of documented deaths, 23.3% were due to NLPHL, whereas most were caused by second primary malignancies or non-malignant conditions.

Taken together, our analysis indicates an excellent efficacy of stage-adapted HL-directed treatment approaches in patients with NLPHL. Therefore, HL-directed therapy can be considered in patients with newly diagnosed NLPHL. However, a reduction of treatment intensity without a significant loss of efficacy should represent the major goal for future studies in this rare disease, given the low lymphoma-specific mortality on one hand and relevant late effects that can be caused by conventional chemotherapy and radiotherapy on the other hand. Possible approaches to achieve this goal could be the implementation of targeted drugs, such as anti-CD20 antibodies and treatment guidance according to interim positron emission tomography.