Mortality in Patients with Endogenous Cushing's Syndrome

Pedram Javanmard, MD[a], Daisy Duan, MD[a], Eliza B. Geer, MD[b,*]

KEYWORDS

• Mortality • Cushing's syndrome • Cushing's disease • Ectopic Cushing's
• Adrenal Cushing's • Subclinical Cushing's

KEY POINTS

- Cushing's syndrome, chronic endogenous cortisol hypersecretion, is associated with an overall increased mortality risk.
- The leading causes of mortality in Cushing's are cardiovascular events, infection, sepsis, and thromboembolism.
- Patients with Cushing's due to a pituitary tumor or a benign adrenal adenoma seem to have the best survival outcomes; persistent or recurrent disease confers high mortality risk.
- Overall, patients with Cushing's due to an ectopic adrenocorticotrophic hormone-secreting tumor or adrenocortical carcinoma have the worst survival rate.
- Prompt diagnosis and treatment of Cushing's and specific monitoring and treatment of comorbidities are paramount to decreasing the burden of mortality.

INTRODUCTION

Endogenous hypercortisolism, known as Cushing's syndrome (CS), is a chronic endocrine disorder caused by excessive adrenal cortisol secretion, with an estimated incidence of 0.7 to 2.4 cases per million population per year.[1–4] The majority (70%) of endogenous CS cases are caused by excess adrenocorticotrophic hormone (ACTH) production from pituitary corticotroph tumors, known as Cushing's disease (CD). ACTH-independent adrenal cortisol production due to an adrenal tumor or hyperplasia is responsible for 20% of CS cases. The remaining 10% of CS cases are due to ectopic ACTH (or very rarely corticotropin-releasing hormone) production.[1–3]

The authors have no relevant disclosures.
[a] Department of Medicine, Division of Endocrinology, Diabetes, and Bone Disease, Icahn School of Medicine, The Mount Sinai Hospital, 1 Gustave L Levy Place, Box 1055, New York, NY 10029, USA; [b] Division of Endocrinology, Department of Medicine, Multidisciplinary Pituitary and Skull Base Tumor Center, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 419, New York, NY 10065, USA
* Corresponding author.
E-mail address: geere@mskcc.org

Endocrinol Metab Clin N Am 47 (2018) 313–333
https://doi.org/10.1016/j.ecl.2018.02.005
endo.theclinics.com

CS can occur at any age. It is, however, more frequent during the fourth to sixth decades of life and more common in women: 79% of pituitary CS, 81% of adrenocortical adenomas, and 60% to 70% of adrenocortical carcinoma (ACC) cases are female, whereas among patients with ectopic CS (ECS), males have an equal or even higher predominance.[5–7]

With regard to the overall predictors for mortality in CS, male gender, older age at diagnosis, overall disease activity duration, disease status (persistent or recurrent disease vs remission), persistent hypercortisolism after initial surgery, and hypertension at last follow-up have been associated with higher mortality risk.[6,8–10] This article reviews the predictors of mortality in patients with endogenous CS. The majority of available mortality data are on patients with CD, and therefore CD is the focus of the review.

ADRENOCORTICOTROPHIC HORMONE-DEPENDENT CUSHING'S DISEASE

CD, due to an ACTH-secreting pituitary corticotroph adenoma, is the most common form of endogenous CS and accounts for 70% of all cases of CS.[3,8,9] In the original series published by Harvey Cushing's in 1932,[11] the median survival in untreated CD was 4.6 years. This finding was validated in a later study[12] that reported a 5-year survival rate of 50%. The main causes of mortality in CD are cardiovascular complications including strokes and myocardial infarctions (**Table 1**).[13,14]

In the past 2 decades, there have been 12 retrospective nationwide or single-center cohort studies that have reported standardized mortality ratios (SMRs) in CD, with 5 of these studies also reporting mortality data on other causes of CS (**Table 2**). Most studies have been conducted in Europe, the United States, or New Zealand, and had median follow-up periods from 6 to 20 years since the onset of treatment. The overall SMR for all-cause mortality in CD ranges from 0.98 to 9.30, indicating that mortality risk in patients with CD is similar to or higher than that of the general population. The majority of these studies further stratify mortality risk based on disease activity status (ie, remission vs recurrent or persistent disease). In addition, several of these studies identify independent mortality risk factors in patients with CD. A limitation of these studies are the small sample sizes, thus, with even smaller numbers of deaths. As several meta-analyses have pointed out, there is also considerable heterogeneity with respect to the definitions of remission, persistence, and recurrence of disease, the timing of the assessment after initial treatment, methods of treatment, and the duration of follow-up periods (**Table 3**). Despite these challenges, there is consistent evidence that persistent CD after pituitary surgery confers the highest risk of mortality, although there are conflicting data regarding mortality risk in patients with disease remission after treatment.

Predictors of Mortality and Risk Factors for Increased Mortality in Patients with Cushing's Disease Overall

Cardiovascular disease results in a 4-fold increase in mortality among patients with persistent CD compared with control populations.[9,15,16] More recent studies suggest a more pronounced mortality risk, with a reported SMR of 13.8 for vascular disease.[17] Some mortality risk may also be present in patients with CD who have been in remission for more than 10 years.[18] In addition, given that the cause of mortality in patients with CD is largely attributed to cardiovascular diseases, certain cardiovascular risk factors have been identified as independent predictors of mortality. The presence of diabetes, but not hypertension, was an independent risk factor for mortality (hazard ratio [HR], 2.82; 95% confidence interval [CI], 1.29–6.17) in 1 study[18]; in other studies,[7,9,17] however, the persistence of both diabetes or glucose metabolism