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INVITED REVIEW

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Long-term morbidity and mortality in patients with Cushing's syndrome

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Abstract

Increased multisystem morbidity and mortality in patients with Cushing's syndrome comprise clinical problems and challenges, both at the time of diagnosis and in remission. Relevant comorbidities and clinical problems include hypertension, diabetes, overweight, myopathy and a high risk for acute complications such as infections and venous thrombembolism. Although there are therapy recommendations for most of these comorbidities, there is a lack of large, prospective studies to confirm and optimise them. Mortality is especially high during active disease and within the first year after diagnosis, as a result of cardiovascular events, infections and suicide. All in all, interdisciplinary therapy management is important for reducing morbidity and mortality over the long-term.

KEYWORDS
ACTH, cortisol, Cushing's disease, hypercortisolism

1 | INTRODUCTION

In 1932, Harvey Cushing described a life-threatening disease[1] in his report of the historically famous case of Minnie G, a patient who most likely suffered from adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome (CS) as a result of an ACTH-secreting adenoma of the pituitary. The patient had most of the clinical signs and comorbidities that we would currently describe as typical of CS: striae, abdominal weight gain, a round face and supraclavicular fat pads. Since Minnie G presented at Harvey Cushing's clinic in 1910, more than 100 years have passed, and major progress in diagnosis and therapy has been made. In this review, we outline the long-term morbidity and mortality in patients with CS.

2 | MORBIDITY

Cushing's syndrome is characterised by a plethora of comorbidities during active disease, as well as after achieving remission (Figure 1). These comorbidities can be life-threatening emergencies or need consideration during the more chronic phase of the disease. In a review, Ragnarsson & Johannsson[2] distinguished three treatment phases when the patient has achieved remission: immediate post-operative management (first weeks), the glucocorticoid dose-tapering phase (1–2 years) and long-term management (the following years). *Immediate post-operative management* includes evaluating the remission state, introducing glucocorticoid replacement therapy and evaluating pituitary function. The following 1–2 years are dominated by the *glucocorticoid dose-tapering* phase and a possible steroid withdrawal syndrome. During the *long-term management phase*, the focus is on the surveillance of chronic comorbidities and the patient's remission status on an annual basis. Cardiovascular risk should be assessed, and related comorbidities (i.e. hypertension, diabetes and dyslipidaemia) must be treated concomitantly. Additionally, bone mineral density should be assessed and treated according to current guidelines. The same applies for psychiatric disorders and cognitive impairments.[2]

A retrospective nationwide registry study from Sweden of 502 patients reported increased standardised incidence ratios (SIRs) for

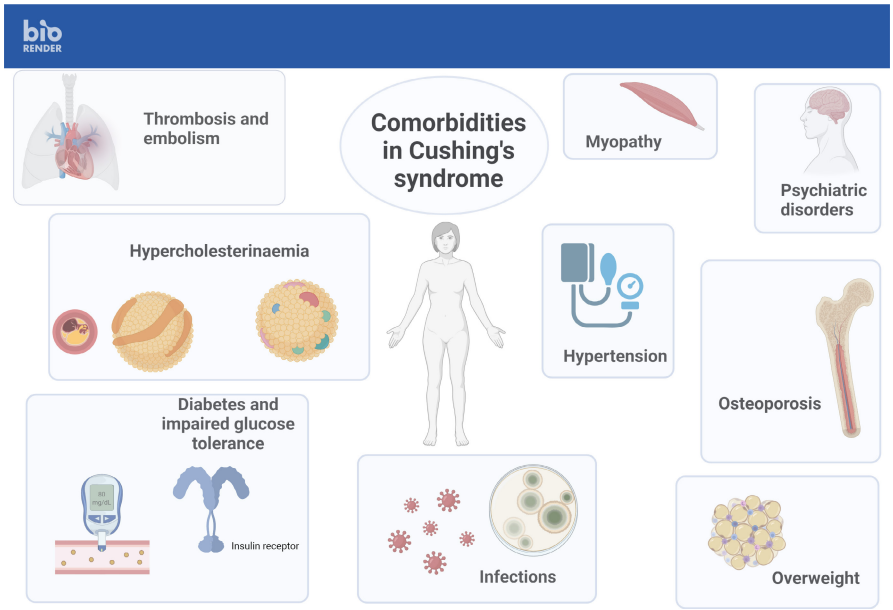

FIGURE 1 The plethora of comorbidities in Cushing's syndrome (created with BioRender.com)

thromboembolism (SIR = 3.4), pulmonary embolism (SIR: 4.4), stroke (SIR: 2.6) and sepsis (SIR: 5.8) during long-term remission.[3] In patients who are not in remission, incidence ratios were even higher for all comorbidities.[3] Another Swedish study with 372 patients addressed the use of psychotropic drugs during long-term remission. The need for antidepressants (odds ratio [OR] = 2.4) and sleeping pills (OR = 3.1) was still increased 5 years after remission compared to the healthy population, whereas the intake of drugs for hypertension (at time of diagnosis, OR = 11.2; in remission, OR = 1.3) and diabetes (at time of diagnosis, OR = 8.1; in remission, OR = 3.1) decreased.[4] These data underline the need for standardised long-term management of these patients.

Several factors influence the persistence of certain long-term comorbidities. For example, lower preoperative urinary free cortisol is associated with the persistence of metabolic comorbidities postoperatively, perhaps because of a longer duration of the disease.[5] Additionally, the number of comorbidities at the time of diagnosis, such as a high body mass index and older age, were predictors of the persistence of comorbidities.[5] Table 1 summarises the frequency and persistence of comorbidities and Table 2 lists the management recommendations for comorbidities.

3 | FREQUENCY AND MANAGEMENT OF SELECTED COMORBIDITIES

3.1 | Hypertension

Arterial hypertension is one of the common comorbidities in patients with CS, affecting up to 85% of patients.[6] Arterial hypertension is also a comorbidity with a relevant impact on mortality risk.[7] The renin–angiotensin–aldosterone system alterations persist even after the normalisation of cortisol levels, independent of blood pressure values.[8] High blood pressure levels during glucocorticoid excess normalise in the majority of patients after curative treatment, especially in young patients.[9] However, the onset and duration of hypertension is relevant for its persistence after the cure of CS, at least in patients with adrenal CS, as shown by Suzuki et al.[10] Schernthaner-Reiter et al.[5], however, reported a resolution of hypertension in only 36% of patients.

3.2 | Diabetes and impaired glucose tolerance

Hyperglycaemia and diabetes are common in patients with CS, affecting approximately 18%–64%.[11-13] Glucose tolerance in CS is influenced by age, genetic predisposition, and the duration and severity of hypercortisolism.[11] A study by Schernthaner-Reiter et al.[5] showed a remission of diabetes in 56% of patients. Similar results were reported by Herndon et al[14]: during 10 months of follow-up, diabetes improved in 47%, resolved in 21% and persisted in 32% of patients. The presence of diabetes is a predictor of worse survival.[15] Beyond anti-diabetic use, there is evidence that the intake of metformin reduces other metabolic complications associated with glucocorticoid excess and affects low-grade inflammation positively.[16] Additionally, metformin appears to have a positive effect on bone density; in patients with CS and those taking metformin, bone density is higher and levels of β-isomerised C-terminal telopeptides are decreased compared to matched patients with CS without metformin intake.[17]

3.3 | Osteoporosis

Reduced bone mass and osteoporotic fractures are hallmarks of CS. A reduced bone density is apparent in 60%–80%,[18] and osteoporosis in up to 50%. Screening for asymptomatic vertebral fractures is recommended because they occur in up to 80% of patients with CS. Bone mass spontaneously improves in the majority of patients within the first 2 years after remission.[19-21] This phase is characterised by a strong increase in both bone formation markers and bone

TABLE 1 Prevalence (partly adapted from Valassi et al.,[6] Sharma et al.[31] and Braun et al.[63]) and persistency of comorbidities

Comorbidity	Prevalence at diagnosis	Studies (first author and year)	Remission and persistency	Open questions
Comorbidities, which (partly) recover				
Hypertension	58%–85%	Valassi 2011[6] Schernthaner-Reiter 2019[5] Suzuki 2000[10]	Persistency in 24%–56% of cases but often very fast improvement after surgery High blood pressure levels pre-surgery are a predictor for persistency in adrenal CS	
Diabetes and impaired glucose tolerance	18%–64%	Giordano 2014[11] Feelders 2012[12] Resmini 2009[13] Schernthaner-Reiter 2019[5] Herndon 2022[14]	Partly improvement within months Improvement in about 56%–68% of patients Persistency in about 1/3 of patients	Do patients with Cushing's syndrome have an increased risk to develop diabetes even after remission?
Bone metabolism: Osteoporosis and fractures	40%–78% osteopenia, 22%–57% osteoporosis Asymptomatic vertebral fractures in up to 80%	Hermus 1995[19] Manning 1992[20] Kawamata 2008[21] Braun 2020[22]	In the majority of patients improvement of bone density within 2 years without specific treatment; osteoporotic fractures are rare after remission[22]	Do patients need a specific therapy for osteroporosis – In general? – If they have fractures at time of diagnosis?
Overweight	Overweight is common at diagnosis (up to 80%), a severe obesity is seldom	Stachowska 2020[39] Braun 2021[40] Lacroix 2020[41] Ceccato 2018[42]	Reversible after cure of disease Medical therapy with pasireotide and metyrapone leads also to weigh reduction One of the first symptoms of recurrence	
Comorbidities, which often persist				
Myopathy	40%–80% of patients are affected	Berr 2017[32] Müller 2019[33] Vogel 2020[27] Vogel 2021[34]	Persists over the long-term In the first 6 months post-surgery, myopathy can temporarily get worse older age, larger waist-to-hip-ratio and higher HbA1c are predictors for myopathy Lower insulin-like growth factor-1 levels post-surgery are a predictor for persistency of myopathy	Is growth hormone therapy useful to improve myopathy?
Psychiatric disorders and cognitive impairment, quality of life	50%–80% depression Reduced quality of life in the majority of patients	For a comprehension summary of studies, see Ragnarsson and Johannsson 2013[2] Quality of life: Zarino 2019[29] Valassi 2018[26] Lindsay 2006[25]	Very often persistency of psychiatric symptoms and cognitive dysfunktion[4,64] Quality of life remains impaired over years in remission, especially in patients with CD	
Infections	Risk for severe infections is increased, frequencies are unknwon	Halem 2017[37] Sarlis 2000[38]	Partly reversible, but mortalitiy as a result of infections remains elevated	Is there a need for pneumocystis jirovecii prophylaxis in every patient?

(Continues)

TABLE 1 (Continued)

Comorbidity	Prevalence at diagnosis	Studies (first author and year)	Remission and persistency	Open questions
Cardiovascular diseases/ Dyslipidemia	40%–70%	Colao 1999[65]	Persistency of increased cardiovascular risk up to 5 years after treatment, persistency of elevated cholsterol levels in about 30% of patients	Which LDL cholesterol cut-off for treatment is reasonable? Should we screen for cardial arrhythmias in every patient? How could cardiovascular risk be reduced in patients with CS in remission?
Thrombosis	Increased risk (10-fold-increase) for thrombosis and stroke, especially in the first year after surgery	For a systematic review please see van der Pas[44]: van der Pas 2013 and 2012[44,45] Manetti 2010[46] Waqar 2021[47]	Persists over years despite remission Especially high shortly after surgery	Who should receive a thromboprophylaxis? In which time period thromboprophylaxis should be administered? –

Abbreviations: CD, Cushing's disease; CS, Cushing's syndrome; LDL, low-density lipoprotein.

TABLE 2 Management: How to deal with:

Comorbidity	Management
Diabetes	– Measurement of HbA1c, insulin and blood glucose at time of diagnosis, consider conducting an oral glucose tolerance test – Start antidiabetic treatment early, most favorable with metformin – Follow the guidelines for treatment of patients with diabetes
Hypertension	– Antihypertensive medical therapy, for example cardioprotective medication (such as ACE-inhibitors, calcium-antagonist or mineralocorticoid receptor antagonists)[9] – Regularly long-term blood pressure measurement – treat to target according to guidelines of AHA[66] and ESC[67]
Osteoporosis	– Measurement of bone density at time of diagnosis and regularly every 2 years, if initially low – Vitamin D intake recommended[68] – Basis therapy: sport, calcium intake via food[68]
Psychiatric disorders	– Assess anxiety, depression and cognitive impairment at time of diagnosis – Psychiatric connection over the long-term is recommended
Cardiovascular risk	– Treat LDL cholesterol to target according to risk assessment – Quit smoking
Myopathy	– Physical exercises – Adequate protein intake
Infections	– Vaccinations against influenza, herpes zoster, pneumococcal disease, COVID-19[69] – Check whether vaccination status is complete but avoid live vaccines in highly immunosuppressed patients – Consider pneumocystis jiroveci pneumonia prophylaxis
Overweight	– Healthy diet – Consider GLP-1 receptor agonists – Physical exercise
Thrombosis	– No clear recommendations available so far – Consider antithrombotic therapy during highly active disease and within the first weeks after surgery – Avoid immobility

Abbreviations: ACE, angiotensin-converting enzyme; AHA, American Heart Association; ESC, European Society of Cardiology; CD, Cushing's disease; CS, Cushing's syndrome; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein.

degradation markers as an indicator of increased bone remodelling.[22] Specific therapy might not be necessary in these patients during early remission and activated bone remodelling,[22] but it has been shown that therapy further improves bone density.[23]

3.4 | Psychiatric disorders and quality of life

Several studies have shown that quality of life is reduced both at the time of diagnosis and during long-term remission,[24,25] with older age and depression at the time of diagnosis as negative predictors of long-term outcome.[26] Additionally, impaired muscle function is associated with reduced quality of life, as shown by data from the German Cushing's registry.[27] Regarding maladaptive personality traits, Tiemensma et al.[28] conducted a study including four frequently-used questionnaires to assess personality traits in patients in remission and a control cohort. Patients with previous CS showed an increased prevalence of psychopathology personality traits.[28] According to a study by Schernthaner-Reiter et al.[5], depression was resolved in 52% of patients in remission. However, in a study by Zarino et al.[29], according to 36-item Short Form Survey (SF-36) scores, depressive symptoms and social introversion persisted in the majority of patients with CS in the first year after surgery.

3.5 | Myopathy

Myopathy is a common and characteristic symptom for patients with CS, affecting 60%–80% of patients.[6,30,31] Typically, proximal muscles are affected. To objectively assess myopathy, a chair-rising test or hand grip strength test might be used.[32] In a cross-sectional study, we showed that hand grip strength was lower at the time of diagnosis (85% that of healthy controls) and that performance in a chair-rising test was impaired (9.5 vs. 7.1 in healthy controls). Even over the long term, myopathy persisted. In a group of patients who were on average 13 years in remission, hand grip strength remained impaired (92% that of healthy controls), and chair-rising test times were impaired, with a mean time of 9.0 s.[32] Müller et al.[33] showed that a polymorphism in the glucocorticoid receptor influences muscle strength and partly explains interindividual differences. Recovery from myopathy, if even present, is slow; post-operatively, a further, temporary worsening of muscle strength was observed, and, afterwards, it slightly increased but remained impaired during long-term follow-up.[27] A few factors influenced the long-term outcome of myopathy: older age, a larger waist-to-hip ratio and a higher HbA1c at the time of diagnosis were independent predictors for long-lasting myopathy.[27] In another study from the German Cushing's registry, we showed that lower insulin-like growth factor (IGF)-1 concentrations 6 months after surgery were associated with an adverse long-term outcome of hypercortisolism-induced myopathy, indicating a role for muscle regeneration after the correction of hypercortisolism.[34] However, preoperative concentrations at the time of diagnosis were not predictive of persistence or recovery of myopathy. Furthermore, the changes in IGF-1 in patients from the time of diagnosis to 6 months after surgery were good predictors of an improvement in grip strength, with significant changes being positive predictors of recovery.[34] Based on these pathophysiological considerations, growth hormone therapy was proposed as a treatment option for myopathy in CS, particularly after transsphenoidal surgery and with an insufficiency of the somatotropic axis, but randomised trials are lacking.[35] Notably, epidemiological data showed an association of growth hormone replacement in patients with CS in remission and improved long-term survival.[36]

3.6 | Infection

Infections are one of the main reasons for the increased mortality in untreated CS, but the risk for severe infections also remains elevated in patients in remission.[3] In a study and review of the literature by van Halem et al.,[37] the occurrence of pneumocystis pneumonia (PCP) in patients with CS was studied. In particular, patients with severe, ectopic CS are affected, and mortality is high. In these patients, chemoprophylaxis is recommended. Interestingly, most patients developed PCP after the initiation of cortisol-lowering therapy. This high risk of infections, especially during the early remission phase, should be kept in mind when curative surgery takes place or medical therapy is administered. Sarlis et al.[38] showed that a very high urinary cortisol level is a predictor for severe infections in patients with ectopic CS.

3.7 | Obesity

Patients with CS often suffer from weight gain and are overweight (up to 80%).[39] Weight gain is also one of the first symptoms of recurrence.[40] After curative surgery, most patients lose weight very quickly. However, detailed studies on the dynamics and to what extent patients lose weight are lacking. Prospective data were collected in trials analysing the effect of pasireotide and metyrapone on body weight and the waist-to-hip-ratio, demonstrating that pasireotide led to weight loss and body fat and waist circumference reduction,[41] whereas metyrapone therapy led to a mean body weight reduction of 4 kg.[42] As in every other patient group, obesity should be treated according to common guidelines, including balanced hypocaloric diets, training, pharmacotherapy and/or even surgery.[43]

3.8 | Thromboembolism

In patients with CS, the risk of developing thrombosis is more than 10-fold increased at the time of diagnosis.[44] A study by van der Pas et al.[45] showed that medical therapy with pasireotide, cabergoline or ketoconazole did not restore the impaired hypercoagulable state. Moreover, the risk for venous thromboembolisms (VTEs) is especially high shortly after curative surgery and remains elevated for several years in comparison to healthy controls.[46] To date, there are

no randomised controlled trials testing the effect of thromboprophylaxis in patients with CS.[44] Therefore, giving thromboprophylaxis during active disease and/or post-operatively remains an individual decision and should be taken into account. According to a study by Waqar et al.[47], chemoprophylaxis with tinzaparin reduced the risk for post-operative VTEs without an increased risk for significant bleeding events.

3.9 | Acute life-threatening complications

The acute complications of patients with endogenous hypercortisolism mainly include vascular events and infections. The risk for VTE, compared to that of the healthy population, is significantly increased. This is true for patients with active disease and for those in biochemical remission. Interestingly, some studies showed an even higher risk, especially within the first year after achieving remission.[48,49] Thirteen studies with 1356 patients with CS, as reviewed by Coelho et al.[50], revealed a VTE incidence rate of 8.9%. A systematic meta-analysis of 48 studies by Wagner et al.[51] found an OR for spontaneous VTE in patients with CS of 17.82 (95% confidence interval [CI] = 15.24–20.85). Moreover, infections are frequent complications in patients with CS. The most prevalent infections were reported as urinary tract infections (29%), skin or soft tissue infections/abscesses (21%), pneumonia (19%) and sepsis (15%).[52] No differences between pituitary and adrenal CS were observed in a nationwide Danish cohort study regarding the risk of acute vascular and infectious complications.[48] However, Stuijver et al.[53] reported an increased post-surgical risk, especially in patients with ACTH-dependent CS, and Suarez et al.[49] observed a further increased risk in patients after bilateral adrenalectomy. Patients with ectopic CS were shown to experience more disease-associated complications.[52] Schernthaner-Reiter et al.[52] recently suggested HbA1c, urinary free cortisol and low-density lipoprotein-cholesterol at the time of diagnosis as independent predictors of the number of overall complications. Interestingly, in their study of 213 patients with benign CS who experienced a total of 300 complications (in 116/213 patients, 54.5% of patients), the incidence rate for acute complications was higher during the post-surgical period (incidence rate 31% prior to surgery compared to 60% 6 months following surgery).[52] Table 3 shows the risk and occurrence of acute complications of CS in each study.

4 | MORTALITY

Cushing's syndrome is associated with increased mortality. In the era before modern treatment options had been introduced, untreated CS was associated with a mortality rate of 50% within 5 years.[54] The increased mortality despite curative surgery arises from both acute life-threatening complications and an overall increased long-term mortality. In a nationwide Danish cohort study, the mortality rate was noticeably higher in CS patients than in an age- and sex-matched control cohort (17.9 vs. 9.5/1000 person-years).[48] The overall hazard ratio (HR) for mortality was 2.3, whereas it was 5.2 in the first year after diagnosis and 2.1 in the subsequent years. These data point to two major determinants influencing mortality in patients with CS: acute life-threatening complications during active CS and within 1 year after the initiation of treatment, and increased long-term mortality because of Cushing-associated multisystem morbidity. Indeed, nationwide studies from New Zealand and Sweden also showed increased overall standardised mortality ratios (SMRs) for patients with CS.[36,55]

5 | OVERALL MORTALITY

Increased overall mortality in patients with CS is primarily determined by markedly higher cardiovascular and infectious disease mortality.[36,48,56,57] This cardiovascular and infectious disease mortality includes mortality as a result of ischaemic heart disease, cerebral infarction, infectious diseases, respiratory diseases (including infections) and diseases of the digestive system (including infections), but an increased rate of suicide was also observed.[36] Some studies reported a particularly increased mortality within the first year after diagnosis and/or the initiation of treatment.[48,58,59] Additionally, Valassi et al.[56] reported in an analysis of 1564 patients in the *European Registry on Cushing's Syndrome* (ERCUSYN) an accumulation of deaths within 90 days from the start of treatment (45% of 49 deceased patients). Here, the most common cause of death was infections, and diabetes mellitus at diagnosis was shown to be more prevalent in deceased patients than in the whole cohort.[56]

Table 4 summarises studies on overall mortality in patients with CS and highlights the respective SMRs and predictors of mortality. However, the data should be interpreted and compared with caution, as some studies were only with patients with Cushing's disease (CD) and others were with patients with CS as a result of pituitary or adrenal adenomas. The remission rates of the patients, if indicated, ranged between 70% and 90% depending on the study. Regarding the patients who were not in remission, in many studies, it was not clear whether these patients had persistent disease or later relapses. Moreover, the follow-up duration and available follow-up data differed between the studies. Overall, the SMR ranged between 0.98 and 9.3, with a consistently higher SMR for cardiovascular diseases (Table 4). Notably, no difference in SMR was found over the last decades in studies that included patients over a long period of time.[36,55] Figure 2 shows the SMRs of the respective studies and the years of publication. Here, and in accordance with the above-mentioned studies, no trend towards an improved outcome is apparent. Predictors of increased mortality were predominantly higher age at the time of diagnosis, disease persistence, impaired glucose metabolism and hypertension (Table 4). A meta-analysis with patients with CD showed an overall SMR of 2.2 (95% CI = 1.5–3.4), whereas patients with persistent disease had a markedly increased SMR of 5.5 (95% CI = 2.7–11.3).[15]

TABLE 3 Acute life-threatening complications

Complication	Study (first author and year)	Cushing cohort	Risk and occurrence of complications	Open questions
VTE	Dekkers 2013[49]	*n* = 343 patients with benign CS	Overall HR = 2.6 (3 years before diagnosis, HR = 8.4; 1 year after diagnosis, HR = 20.6; 1–30 years after diagnosis, HR = 1.6)	Which patients are at increased risk and should therefore be monitored and/or treated? For whom and in what dose should thromboprophylaxis be given during active CS and in the postoperative period?
	Schernthaner-Reiter 2021[54]	*n* = 213 patients with benign CS	Incidence 16.9% of patients, more frequent during active hypercortisolism than afterwards	
	Papakokkinou 2020[3]	*n* = 502 patients with CD	Overall SIR for pulmonary embolism 4.9 (1 year after remission, SIR = 24.2; long-term remission, SIR = 5.2) and overall SIR for deep vein thrombosis 3.4 (3 years before diagnosis, SIR = 13.8; 1 year after remission, SIR = 13.0; long-term remission, SIR = 4.6)	
	Stuijver 2011[55]	*n* = 473 patients with benign CS	37 of 473 patients experienced VTE during the study period, resulting in an overall incidence of 14.6 per 1000 person-years	
	Manetti 2010[46]	*n* = 40 patients with benign CS	Occurrence in 7.5% (3 of 40 patients; one before surgery and two in the early postoperative period)	
Infections	Dekkers 2013[49]	*n* = 343 patients with benign CS	Overall HR = 4.9 (3 years before diagnosis, HR = 2.6; 1 year after diagnosis, HR = 22.3; 1–30 years after diagnosis, HR = 3.7)	Which patients are at increased risk and should therefore be monitored and/or treated? Should *Pneumocystis jiroveci* pneumonia be given in general? How can the risk of infection be reduced during active disease, but also in the postoperative period?
	Papakokkinou 2020[3]	*n* = 502 patients with CD	Overall SIR for sepsis 6.7 (1 year after remission, SIR = 13.6; long-term remission, SIR = 6.0)	
	Schernthaner-Reiter 2021[54]	*n* = 213 patients with benign CS	Most frequent complication in this study, with an occurrence of 25.4%, equally distributed between active hypercortisolism and after surgery	
Acute myocardial infarction	Dekkers 2013[49]	*n* = 343 patients with benign CS	Overall HR = 3.7 (3 years before diagnosis, HR = 2.2; 1 year after diagnosis, HR = 4.5; 1–30 years after diagnosis, HR = 3.6)	Which patients are at particularly increased cardiovascular risk? How can cardiovascular risk be reduced for Cushing's patients in the long-term? How should the risk factors be adjusted?
	Papakokkinou 2020[3]	*n* = 502 patients with CD	Overall SIR = 1.9	
	Schernthaner-Reiter 2021[54]	*n* = 213 patients with benign CS	Occurrence of acute coronary events in 3% of patients	
Stroke	Dekkers 2013[49]	*n* = 343 patients with benign CS	Overall HR = 2.0 (3 years before diagnosis, HR = 5.0; 1 year after diagnosis, HR = 6.5; 1–30 years after diagnosis, HR = 1.8)	
	Papakokkinou 2020[3]	*n* = 502 patients with CD	Overall SIR = 3.0 (3 years before diagnosis, SIR = 3.0; 1 year after remission, SIR = 4.9; long-term remission, SIR = 3.1)	

Abbreviations: CS, Cushing's syndrome; HR, hazard ratio; SIR, standardized incidence ratio; VTE, venous thromboembolism.

TABLE 4 Overall mortality in patients with Cushing's syndrome

Study (first author and year)	Patient time period	Cushing cohort	Relative mortality risk	Determinants of mortality by study
Etxabe 1994[70]	1975–1992	*n* = 49 patients with CD, of whom five died within FU	SMR = 3.8 (95% CI = 2.5–17.9) – SMR for CV diseases 5.0 (95% CI = 3.4–48.6)	Higher age, hypertension, impaired glucose metabolism
Swearingen 1999[71]	1978–1996	*n* = 161 patients with CD, of whom six died within FU	SMR = 0.98 (95% CI = 0.44–2.2)	
Lindholm 2001[59]	1985–1995	*n* = 139 patients with CS, of whom 23 died within FU	SMR = 3.68 (95% CI = 2.34–5.33)	Persistence of disease; excess mortality was noted within the first year after the initial admission for hypercortisolism
Hammer 2004[58]	1975–1998	*n* = 289 patients with CD, of whom 25 died within FU	SMR = 1.42 (95% CI = 0.95–2.10)	Initial persistent disease
Dekkers 2007[72]	1977–2005	*n* = 74 patients with CD, of whom 12 died within FU	SMR = 2.39 (95% CI = 1.22–3.90)	Persistence of disease
Bolland 2011[50]	1960–2005	*n* = 253 patients with CS, of whom 36 died within FU	SMR = 4.1 (95% CI = 2.9–5.7)	Biochemical cure, hypertension
Clayton 2011[15]	1960–2009	*n* = 60 patients with CD, of whom 13 died within FU	SMR = 4.8 (95% CI = 2.8–8.3) – SMR for CV diseases 13.8 (95% CI = 7.2–36.5)	Persistence of disease, older age at diagnosis, hypertension, diabetes
Hassan-Smith 2012[73]	1988–2009	*n* = 80 patients with CD, of whom 13 died within FU	SMR = 3.17 (95% CI = 1.70–5.43)	Persistent/recurrent disease
Yaneva 2013[57]	1965–2010	*n* = 335 patients with CS, of whom 80 died within FU	SMR = 2.22 (95% CI = 1.06–4.08)	Active disease, age, male sex, etiology of the disease, overall duration of active disease
Ntali 2013[74]	1967–2009	*n* = 182 patients with CD, of whom 26 died within FU *n* = 16 patients with adrenal CS, of whom one died within FU	SMR for CD 9.3 (95% CI = 6.2–13.4) SMR for adrenal CS 5.3 (95% CI = 0.3–26.0)	Age at diagnosis (for CD)
Dekkers 2013[49]	1980–2010	*n* = 343 patients with CS, of whom 74 died within FU	HR for mortality 2.3 (95% CI = 1.8–2.9)	Higher HR for mortality in the first year after diagnosis than in subsequent years (HR = 5.2 vs. 2.1)
Ragnarsson 2019[36]	1987–2013	*n* = 502 patients with CD, of whom 133 died within FU	SMR = 2.5 (95% CI = 2.1–2.9) – SMR for CV diseases 3.3 (95% CI = 2.6–4.3) – SMR for infectious diseases 5.1 (95% CI = 1.4–13.0) – SMR for respiratory diseases 2.8 (95% CI = 1.3–5.3) – SMR for gastrointestinal diseases 4.8 (95% CI = 2.2–9.1)	Persistent disease, higher age; *increased mortality (patients in remission)*: bilateral adrenalectomy and glucocorticoid replacement; *improved outcome (patients in remission)*: growth hormone replacement
Roldán-Sarmiento 2020[75]	1979–2018	*n* = 191 patients with CD, of whom 18 died within FU	SMR = 3.1 (95% CI = 1.9–4.8) – SMR for CV diseases 4.2 (95% CI = 1.5–9.3)	Diabetes, higher cortisol levels at diagnosis, active disease
Pikkarainen [76]	1981–1994	*n* = 63 patients with CS, of whom eight died within FU	SMR = 2.02 (95% CI = 0.87–3.96)	

Abbreviations: CI, confidence interval; CD, Cushing's disease; CS, Cushing's syndrome; CV, cardiovascular; FU, follow-up; HR, hazard ratio; SMR, standardised mortality ratio.

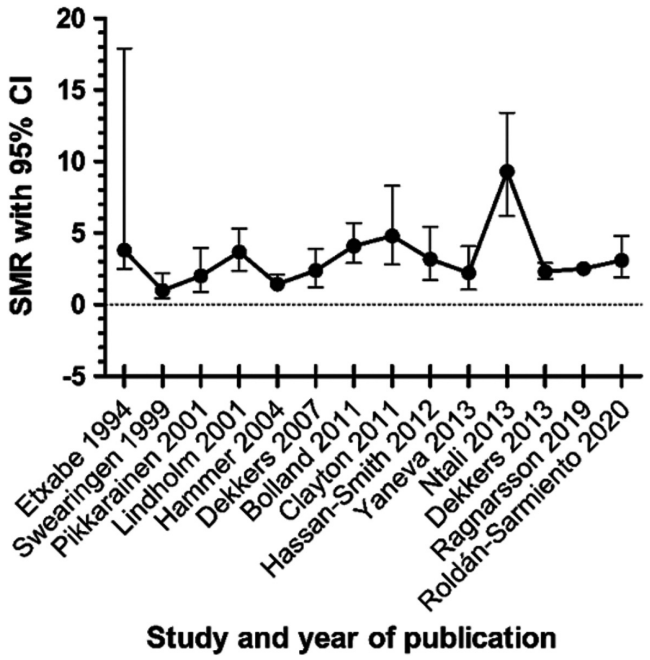

FIGURE 2 Overall mortality by study and year of publication. CI, confidence interval; SMR, standardised mortality ratio

6 | INCREASED MORTALITY DESPITE BIOCHEMICAL REMISSION

Despite curative therapy leading to biochemical remission, increased long-term mortality was reported. A meta-analysis by Van Haalen et al.[60] revealed that the SMR for patients with CD in remission remained elevated, with a pooled SMR of 2.5 (95% CI = 1.4–4.2). An increased SMR for patients with CD in remission was also shown in a study by Clayton et al.[61] with 320 patients. They found an SMR for all-cause mortality of 1.61 (95% CI = 1.23–2.12) despite these patients having achieved remission more than 10 years prior, which still indicates a 61% increased mortality risk. The SMR for circulatory diseases was even higher (2.72; 95% CI = 1.88–3.95). Factors influencing mortality reported in this study were the presence of diabetes (HR = 2.82) and the number of treatments (HR = 1.77 for two treatments and HR = 2.6 for three treatments).[61] In the Swedish nationwide study by Ragnarsson et al.,[36] the SMR for patients with CD in remission was also increased (1.9; 95% CI = 1.5–2.3). Interestingly, in these patients, growth hormone replacement was found to be associated with improved outcome, whereas bilateral adrenalectomy and glucocorticoid replacement therapy were associated with increased mortality. Notably, time from diagnosis to remission was not associated with mortality risk, and the HR of mortality for patients receiving < 25 mg of hydrocortisone was not different from that of patients receiving ≥ 25 mg of hydrocortisone.[36]

7 | PERSPECTIVE

Despite many improvements in diagnostic and therapeutic options, the overall mortality in patients with CS remains markedly elevated. Because most studies associate remission status with improved survival, patients with CS need life-long surveillance for recurrence and for adequate management of comorbidities. Persistent metabolic comorbidities have been further associated with increased mortality, and cardiovascular diseases play a major role in overall mortality risk. Therefore, regular and strict management of cardiovascular risk factors is necessary. Especially in the early remission phase, an increased risk of life-threatening complications has been reported for patients with CS. Ongoing medical observation of these patients is therefore crucial, both during active CS and in the post-operative phase, to detect complications at an early stage and to be able to treat them accordingly. The underlying mechanisms of acute complications and increased long-term mortality despite remission are poorly understood. Therefore, in the new consensus and guideline update of CD published in 2021 in *The Lancet Diabetes & Endocrinology*, the optimisation of the management of complications was identified as one of the highest priority research issues for the future.[62]

This article is part of an update series on the diagnosis and treatment of Cushing's syndrome.[77–94]

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Leah T. Braun: Visualization; Writing – original draft. **Frederick Vogel:** Visualization; Writing – original draft. **Martin Reincke:** Supervision; Writing – review & editing.

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DATA AVAILABILITY

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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REFERENCES

1. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (*Pituitary basophilism*). *Bull Johns Hopkins Hosp*. 1932;50:137-195.
2. Ragnarsson O, Johannsson G. Cushing's syndrome: a structured short- and long-term management plan for patients in remission. *Eur J Endocrinol*. 2013;169(5):R139-R152.
3. Papakokkinou E, Olsson DS, Chantzichristos D, et al. Excess morbidity persists in patients with Cushing's disease during long-term remission: a Swedish nationwide study. *J Clin Endocrinol Metab*. 2020;105(8):2616-2624.
4. Bengtsson D, Ragnarsson O, Berinder K, et al. Psychotropic drugs in patients with Cushing's disease before diagnosis and at

long-term follow-up: a nationwide study. *J Clin Endocrinol Metab*. 2021;106(6):1750-1760.
5. Schernthaner-Reiter MH, Siess C, Gessl A, et al. Factors predicting long-term comorbidities in patients with Cushing's syndrome in remission. *Endocrine*. 2019;64(1):157-168.
6. Valassi E, Santos A, Yaneva M, et al. The European registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *Eur J Endocrinol*. 2011;165(3):383-392.
7. Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD, Geer EB. Predictors of mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. *J Clin Endocrinol Metab*. 2013;98(3):1022-1030.
8. van der Pas R, van Esch JH, de Bruin C, et al. Cushing's disease and hypertension: in vivo and in vitro study of the role of the renin-angiotensin-aldosterone system and effects of medical therapy. *Eur J Endocrinol*. 2014;170(2):181-191.
9. Isidori AM, Graziadio C, Paragliola RM, et al. The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications. *J Hypertens*. 2015;33(1):44-60.
10. Suzuki T, Shibata H, Ando T, et al. Risk factors associated with persistent postoperative hypertension in Cushing's syndrome. *Endocr Res*. 2000;26(4):791-795.
11. Giordano C, Guarnotta V, Pivonello R, et al. Is diabetes in Cushing's syndrome only a consequence of hypercortisolism? *Eur J Endocrinol*. 2014;170(2):311-319.
12. Feelders RA, Pulgar SJ, Kempel A, Pereira AM. The burden of Cushing's disease: clinical and health-related quality of life aspects. *Eur J Endocrinol*. 2012;167(3):311-326.
13. Resmini E, Minuto F, Colao A, Ferone D. Secondary diabetes associated with principal endocrinopathies: the impact of new treatment modalities. *Acta Diabetol*. 2009;46(2):85-95.
14. Herndon J, Kaur RJ, Romportl M, et al. The effect of curative treatment on hyperglycemia in patients with cushing syndrome. *J Endocr Soc*. 2022;6(1):bvab169.
15. Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *J Clin Endocrinol Metab*. 2011;96(3):632-642.
16. Pernicova I, Kelly S, Ajodha S, et al. Metformin to reduce metabolic complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial. *Lancet Diabetes Endocrinol*. 2020;8(4):278-291.
17. Vogel F, Braun L, Rubinstein G, et al. Metformin and bone metabolism in endogenous glucocorticoid excess: an exploratory study. *Front Endocrinol*. 2021;12:765067.
18. Toth M, Grossman A. Glucocorticoid-induced osteoporosis: lessons from Cushing's syndrome. *Clin Endocrinol*. 2013;79(1):1-11.
19. Hermus AR, Smals AG, Swinkels LM, et al. Bone mineral density and bone turnover before and after surgical cure of Cushing's syndrome. *J Clin Endocrinol Metab*. 1995;80(10):2859-2865.
20. Manning PJ, Evans MC, Reid IR. Normal bone mineral density following cure of Cushing's syndrome. *Clin Endocrinol*. 1992;36(3):229-234.
21. Kawamata A, Iihara M, Okamoto T, Obara T. Bone mineral density before and after surgical cure of Cushing's syndrome due to adrenocortical adenoma: prospective study. *World J Surg*. 2008;32(5):890-896.
22. Braun LT, Fazel J, Zopp S, et al. The effect of biochemical remission on bone metabolism in Cushing's syndrome: a 2-year follow-up study. *J Bone Miner Res*. 2020;35(9):1711-1717.
23. Di Somma C, Colao A, Pivonello R, et al. Effectiveness of chronic treatment with alendronate in the osteoporosis of Cushing's disease. *Clin Endocrinol*. 1998;48(5):655-662.
24. Lindholm J, Juul S, Jorgensen J, et al. Incidence and late prognosis of Cushing's syndrome: a population-based study. *J Clin Endocrinol Metab*. 2001;86:117-123.
25. Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. *J Clin Endocrinol Metab*. 2006;91(2):447-453.
26. Valassi E, Feelders R, Maiter D, et al. Worse health-related quality of life at long-term follow-up in patients with Cushing's disease than patients with cortisol producing adenoma. Data from the ERCUSYN. *Clin Endocrinol*. 2018;88(6):787-798.
27. Vogel F, Braun LT, Rubinstein G, et al. Persisting muscle dysfunction in Cushing's syndrome despite biochemical remission. *J Clin Endocrinol Metab*. 2020;105(12):e4490-e4498.
28. Tiemensma J, Biermasz NR, Middelkoop HA, van der Mast RC, Romijn JA, Pereira AM. Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushings's disease. *J Clin Endocrinol Metab*. 2010;95(10):E129-E141.
29. Zarino B, Verrua E, Ferrante E, et al. Cushing's disease: a prospective case-control study of health-related quality of life and cognitive status before and after surgery. *J Neurosurg*. 2019;1-11. doi:10.3171/2019.8.JNS19930
30. Newell-Price J, Grossman A. Diagnosis and management of Cushing's syndrome. *Lancet*. 1999;353(9170):2087-2088.
31. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clin Epidemiol*. 2015;7:281.
32. Berr CM, Stieg MR, Deutschbein T, et al. Persistence of myopathy in Cushing's syndrome: evaluation of the German Cushing's registry. *Eur J Endocrinol*. 2017;176(6):737-746.
33. Müller LM, Kienitz T, Deutschbein T, et al. Glucocorticoid receptor polymorphisms influence muscle strength in Cushing's syndrome. *J Clin Endocrinol Metab*. 2020;105(1):305-313.
34. Vogel F, Braun L, Rubinstein G, et al. Patients with low IGF-I after curative surgery for Cushing's syndrome have an adverse long-term outcome of hypercortisolism-induced myopathy. *Eur J Endocrinol*. 2021;184(6):813-821.
35. Reincke M. Cushing syndrome associated myopathy: it is time for a change. *Endocrinol Metab*. 2021;36(3):564-571.
36. Ragnarsson O, Olsson DS, Papakokkinou E, et al. Overall and disease-specific mortality in patients with Cushing disease: a Swedish nationwide study. *J Clin Endocrinol Metab*. 2019;104(6):2375-2384.
37. van Halem K, Vrolijk L, Pereira AM, de Boer MGJ. Characteristics and mortality of pneumocystis pneumonia in patients with Cushing's syndrome: a plea for timely initiation of chemoprophylaxis. *Open Forum Infect Dis*. 2017;4(1):ofx002.
38. Sarlis NJ, Chanock SJ, Nieman LK. Cortisolemic indices predict severe infections in Cushing syndrome due to ectopic production of adrenocorticotropin. *J Clin Endocrinol Metab*. 2000;85(1):42-47.
39. Stachowska B, Kuliczkowska-Płaksej J, Kałużny M, Grzegrzółka J, Jończyk M, Bolanowski M. Etiology, baseline clinical profile and comorbidities of patients with Cushing's syndrome at a single endocrinological center. *Endocrine*. 2020;70(3):616-628.
40. Braun LT, Zopp S, Vogel F, et al. Signs, symptoms and biochemistry in recurrent Cushing disease: a prospective pilot study. *Endocrine*. 2021;73(3):762-766.
41. Lacroix A, Bronstein MD, Schopohl J, et al. Long-acting pasireotide improves clinical signs and quality of life in Cushing's disease: results from a phase III study. *J Endocrinol Invest*. 2020;43(11):1613-1622.
42. Ceccato F, Zilio M, Barbot M, et al. Metyrapone treatment in Cushing's syndrome: a real-life study. *Endocrine*. 2018;62(3):701-711.
43. Yumuk V, Tsigos C, Fried M, et al. European guidelines for obesity management in adults. *Obes Facts*. 2015;8(6):402-424.
44. van der Pas R, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clin Endocrinol*. 2013;78(4):481-488.

45. van der Pas R, de Bruin C, Leebeek FW, et al. The hypercoagulable state in Cushing's disease is associated with increased levels of procoagulant factors and impaired fibrinolysis, but is not reversible after short-term biochemical remission induced by medical therapy. *J Clin Endocrinol Metab*. 2012;97(4):1303-1310.
46. Manetti L, Bogazzi F, Giovannetti C, et al. Changes in coagulation indexes and occurrence of venous thromboembolism in patients with Cushing's syndrome: results from a prospective study before and after surgery. *Eur J Endocrinol*. 2010;163(5):783-791.
47. Waqar M, Chadwick A, Kersey J, et al. Venous thromboembolism chemical prophylaxis after endoscopic trans-sphenoidal pituitary surgery. *Pituitary*. 2022;25:267-274.
48. Dekkers OM, Horváth-Puhó E, Jørgensen JO, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *J Clin Endocrinol Metab*. 2013;98(6):2277-2284.
49. Suarez MG, Stack M, Hinojosa-Amaya JM, et al. Hypercoagulability in Cushing syndrome, prevalence of thrombotic events: a large, single-center, retrospective study. *J Endocr Soc*. 2020;4(2):bvz033.
50. Coelho MC, Santos CV, Vieira Neto L, Gadelha MR. Adverse effects of glucocorticoids: coagulopathy. *Eur J Endocrinol*. 2015;173(4):M11-M21.
51. Wagner J, Langlois F, Lim DST, McCartney S, Fleseriu M. Hypercoagulability and risk of venous thromboembolic events in endogenous Cushing's syndrome: a systematic meta-analysis. *Front Endocrinol*. 2018;9:805.
52. Schernthaner-Reiter MH, Siess C, Micko A, et al. Acute and life-threatening complications in Cushing syndrome: prevalence, predictors, and mortality. *J Clin Endocrinol Metab*. 2021;106(5):e2035-e2046.
53. Stuijver DJ, van Zaane B, Feelders RA, et al. Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. *J Clin Endocrinol Metab*. 2011;96(11):3525-3532.
54. Plotz CM, Knowlton AI, Ragan C. The natural history of Cushing's syndrome. *Am J Med*. 1952;13(5):597-614.
55. Bolland MJ, Holdaway IM, Berkeley JE, et al. Mortality and morbidity in Cushing's syndrome in New Zealand. *Clin Endocrinol*. 2011;75(4):436-442.
56. Valassi E, Tabarin A, Brue T, et al. High mortality within 90 days of diagnosis in patients with Cushing's syndrome: results from the ERCUSYN registry. *Eur J Endocrinol*. 2019;181(5):461-472.
57. Yaneva M, Kalinov K, Zacharieva S. Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center. *Eur J Endocrinol*. 2013;169(5):621-627.
58. Hammer GD, Tyrrell JB, Lamborn KR, et al. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *J Clin Endocrinol Metab*. 2004;89(12):6348-6357.
59. Lindholm J, Juul S, Jørgensen JO, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. *J Clin Endocrinol Metab*. 2001;86(1):117-123.
60. van Haalen FM, Broersen LH, Jorgensen JO, Pereira AM, Dekkers OM. Management of endocrine disease: mortality remains increased in Cushing's disease despite biochemical remission: a systematic review and meta-analysis. *Eur J Endocrinol*. 2015;172(4):R143-R149.
61. Clayton RN, Jones PW, Reulen RC, et al. Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4(7):569-576.
62. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847-875.
63. Braun LT, Riester A, Oßwald-Kopp A, et al. Toward a diagnostic score in Cushing's syndrome. *Front Endocrinol*. 2019;10:766.
64. Papakokkinou E, Johansson B, Berglund P, Ragnarsson O. Mental fatigue and executive dysfunction in patients with Cushing's syndrome in remission. *Behav Neurol*. 2015;2015:173653.
65. Colao A, Pivonello R, Spiezia S, et al. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. *J Clin Endocrinol Metab*. 1999;84(8):2664-2672.
66. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71(19):e127-e248.
67. Committee G. 2003 European society of hypertension-European society of cardiology guidelines for the management of arterial hypertension. *J Hypertens*. 2003;21(6):1011-1053.
68. Scillitani A, Mazziotti G, Di Somma C, et al. Treatment of skeletal impairment in patients with endogenous hypercortisolism: when and how? *Osteoporos Int*. 2014;25(2):441-446.
69. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831.
70. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clin Endocrinol*. 1994;40(4):479-484.
71. Swearingen B, Biller BM, Barker FG 2nd, et al. Long-term mortality after transsphenoidal surgery for Cushing disease. *Ann Intern Med*. 1999;130(10):821-824.
72. Dekkers OM, Biermasz NR, Pereira AM, et al. Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab*. 2007;92(3):976-981.
73. Hassan-Smith ZK, Sherlock M, Reulen RC, et al. Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years. *J Clin Endocrinol Metab*. 2012;97(4):1194-1201.
74. Ntali G, Asimakopoulou A, Siamatras T, et al. Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. *Eur J Endocrinol*. 2013;169(5):715-723.
75. Roldán-Sarmiento P, Lam-Chung CE, Hinojosa-Amaya JM, et al. Diabetes, active disease, and afternoon serum cortisol levels predict Cushing's disease mortality: a cohort study. *J Clin Endocrinol Metab*. 2021;106(1):e103-e111.
76. Pikkarainen L, Sane T, Reunanen A. The survival and well-being of patients treated for Cushing's syndrome. *J Intern Med*. 1999;245(5):463-468. doi:10.1046/j.1365-2796.1999.00483.x
77. Millar RP, Karavitaki N, Kastelan D. Cushing's syndrome update: 100 years after Minnie G. *J Neuroendocrinol*. 2022;34(8):e13167. doi:10.1111/jne.13167
78. Clayton RN. Cardiovascular complications of Cushings Syndrome: impact on morbidity and mortality. *J Neuroendocrinol*. 2022;34(8):e13175. doi:10.1111/jne.13175
79. Honegger J, Nasi-Kordhishti I. Surgery and perioperative management of patients with Cushing's disease. *J Neuroendocrinol*. 2022;34(8):e13177. doi:10.1111/jne.13177
80. Balomenaki M, Margaritopoulos D, Vassiliadi DA, Tsagarakis S. Diagnostic workup of Cushing's syndrome. *J Neuroendocrinol*. 2022;34(8):e13111. doi:10.1111/jne.13111
81. Braun LT, Vogel F, Reincke M. Long-term morbidity and mortality in patients with Cushing's syndrome. *J Neuroendocrinol*. 2022;34(8):e13113. doi:10.1111/jne.13113
82. Valassi E. Clinical presentation and etiology of Cushing's syndrome: Data from ERCUSYN. *J Neuroendocrinol*. 2022;34(8):e13114. doi:10.1111/jne.13114
83. Hamblin R, Coulden A, Fountas A, Karavitaki N. The diagnosis and management of Cushing's syndrome in pregnancy. *J Neuroendocrinol*. 2022;34(8):e13118. doi:10.1111/jne.13118
84. Castinetti F. Medical management of Cushing's disease: When and how? *J Neuroendocrinol*. 2022;34(8):e13120. doi:10.1111/jne.13120
85. Bonneville J-F, Potorac I, Petrossians P, Tshibanda L, Beckers A. Pituitary MRI in Cushing's disease - an update. *J Neuroendocrinol*. 2022;34(8):e13123. doi:10.1111/jne.13123

86. Losa M, Albano L, Bailo M, Barzaghi LR, Mortini P. Role of radiosurgery in the treatment of Cushing's disease. *J Neuroendocrinol*. 2022;34(8):e13134. doi:10.1111/jne.13134
87. Hayes AR, Grossman AB. Distinguishing Cushing's disease from the ectopic ACTH syndrome: Needles in a haystack or hiding in plain sight? *J Neuroendocrinol*. 2022;34(8):e13137. doi:10.1111/jne.13137
88. Dekkers AJ, Amaya JM, van der Meulen M, Biermasz NR, Meijer OC, Pereira AM. Long-term effects of glucocorticoid excess on the brain. *J Neuroendocrinol*. 2022;34(8):e13142. doi:10.1111/jne.13142
89. Salehidoost R, Korbonits M. Glucose and lipid metabolism abnormalities in Cushing's syndrome. *J Neuroendocrinol*. 2022;34(8):e13143. doi:10.1111/jne.13143
90. Simon J, Theodoropoulou M. Genetics of Cushing's disease. *J Neuroendocrinol*. 2022;34(8):e13148. doi:10.1111/jne.13148
91. Lasolle H, Vasiljevic A, Jouanneau E, Ilie MD, Raverot G. Aggressive corticotroph tumors and carcinomas. *J Neuroendocrinol*. 2022;34(8):e13169. doi:10.1111/jne.13169
92. Balasko A, Zibar Tomsic K, Kastelan D, Dusek T. Hypothalamic–pituitary–adrenal axis recovery after treatment of Cushing's syndrome. *J Neuroendocrinol*. 2022;34(8):e13172. doi:10.1111/jne.13172
93. Drouin J. The corticotroph cells from early development to tumorigenesis. *J Neuroendocrinol*. 2022;34(8):e13147. doi:10.1111/jne.13147
94. Guignat L, Bertherat J. Long-term follow-up and predictors of recurrence of Cushing's disease. *J Neuroendocrinol*. 2022;34(8):e13186. doi:10.1111/jne.13186

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