Impact of Glucocorticoid Use on Mortality in Adults with Chronic Diseases: A Systematic Literature Review

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INTRODUCTION

- Although >50 million adults worldwide use glucocorticoids (GCs) long term,[1,2] there is insufficient evidence quantifying mortality risk
- Despite the availability of steroid-sparing medications, there is evidence that GC use has increased[2]
- GCs are used to treat a variety of inflammatory, allergic, and autoimmune disorders[3]

OBJECTIVE

The goal of this systematic literature review (SLR) was to characterize the impact of long-term GC therapy (defined as ≥3 months) on mortality

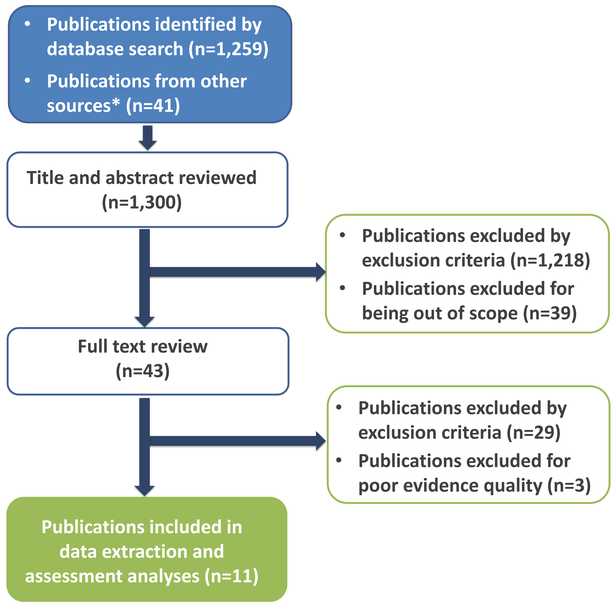
METHOD

- Relevant, English-language publications (January 2012-December 2022) were identified from MEDLINE, EMBASE, NHS Economic Evaluation, Cochrane, and other search engines
  - ➢ Scope of the study was predefined by criteria in **Table 1**
  - ➢ 2 independent reviewers assessed publications for inclusion in analysis
- Outcomes were stratified by clinical consequences of GC use
- Mortality rates of GC users vs nonusers were analyzed, independent of baseline condition
  - ➢ Association between use of GC and mortality was estimated through hazard ratios (HRs), mortality rate, and relative risk (RR) of death

Table 1. Systematic literature search eligibility criteria

PICOS framework	Inclusion criteria	Exclusion criteria
Patient population	• Adult patients (≥18 years) with long-term GC use (≥3 months)	• Non-human studies • Short-term GC use (<3 months) • Oncology population
Intervention	• Systemic GCs (oral or intravenous)	• Non-systemic GCs (topical, inhaled, perineural, or neuro-axial)
Comparator	• Non-GC users (ie, placebo, best supportive care) with same underlying disease	• Comparison between GC medications • Comparison of GC users with a baseline condition vs healthy patients or other disease
Outcomes	• Mortality or death	• Lack of relevant data on outcomes of interest and other adverse event data
Study design	• Randomized controlled trials (RCTs) • Quasi experiments • Pre-/post-observational cohort studies • Cross-sectional studies	• SLRs and meta-analysis • Clinical guidelines • No abstract or full-text to inform decision • Press release • Letters to editor • Pharmacokinetic or pharmacodynamic studies

Figure 1. PRISMA chart for survival analysis



*Additional relevant publications were identified and retrieved from other sources, including Google Scholar, Opengrey, Clinicaltrials.gov, the World Health Organization clinical trial registry, bibliographies of relevant identified studies, and 2019 conference proceedings not indexed in Embase.

Table 2. Summary table of GC use impact on mortality

Study	Condition Study design	GC (Y/N)	GC Dose	HR mortality (95% CI) vs no-GC use	RR death (CI) vs no-GC use	Mortality rate (per 1000 PY)
ASTHMA						
Ekstrom et al. 2019[4]	Asthma (observational, prospective study)	Y	≥5 mg/day	1.34 (1.24-1.45)	-	-
		Y	<5 mg/day	0.95 (0.91-0.99)	-	-
		N	NA	Reference	-	-
Lee et al. 2019[5]	Asthma (observational, retrospective study)	Y	<5 mg/day	1.84 (1.69-2.00)	-	-
		Y	≥10 mg/day	2.56 (2.35-2.80)	-	-
		Y	All doses	2.17 (2.04-2.31)	-	-
		N	No GC group	Reference	-	-
RHEUMATOID ARTHRITIS						
Ajeganova et al. 2014[6]	RA (observational, prospective study)	Y	7.5 mg/day	1.6 (0.6-4.1)	-	-
		N	NA	Reference	-	-
del Rincon et al. 2014[7]	RA (observational, retrospective study)	Y	Mean daily GC dose 6.9 mg (5.0)	-	1.77 (1.36-2.32)	-
		N	No GC users	Reference	-	-
		Y	Daily dose <5 mg/day	1.19 (0.74-1.90)	-	-
		Y	Daily dose 5-7 mg/day	1.21 (0.88-1.66)	-	-
		Y	Daily dose 8-15 mg/day	1.78 (1.22-2.60)	-	-
		Y	Daily dose ≥15 mg/day	2.83 (1.41-5.66)	-	-
Iqbal et al. 2017[8]	RA (observational, retrospective study)	Y	At least 5 mg/day minimum 3 months	-	1.47 (1.05-2.05)	-
		N	NA	-	1.05 (0.68-1.63)	-
Lacaille et al. 2014[9]	RA (observational case control study)	N	Non-GC users	Reference	-	-
		Y	Per 5 mg of current dose	1.22 (1.21-1.24)	-	-
Movahedi et al. 2016[10]	RA (observational, retrospective cohort study)	Y	GC users mean daily dose 7.5 mg	1.97 (1.81-2.15)	-	44 (42.1–46.0)
		N	No GC users	Reference	-	15.5 (14.6–16.5)
		Y	Current GC use overall	1.77 (1.62-1.93)	-	-
		Y	Current GC dose >0 to 4.9 mg	1.02 (0.87-1.20)	-	-
		Y	Current GC dose 5.0 to 7.4 mg	1.44 (1.26-1.64)	-	-
		Y	Current GC dose 7.5 to 14.9 mg	2.24 (1.98-2.54)	-	-
		Y	Current GC dose 15.0 to 24.9 mg	4.5 (3.61-5.62)	-	-
		Y	Current GC dose ≥25 mg	11 (8.87-13.6)	-	-
Wasko et al. 2016[11]	RA (observational, retrospective longitudinal study)	Prednisolone w propensity score adjustment, median dose 5mg/day, IQR (5 to 10 mg)		2.83 (1.03-7.76)	-	-
		Prednisolone use – IPTW		1.75 (1.49-2.04)	-	-
		Prednisolone vs prednisolone + methotrexate OR neither		2.95 (1.07-8.10)	-	-
		Prednisolone alone compared to prednisolone + sulfasalazine		2.99 (1.09-8.17)	-	-
MULTIPLE CONDITIONS/MISCELLANEOUS						
Mebrahtu et al. 2019[12]	Giant cell arteritis, polymyalgia rheumatica, IBS, RA, SLE and/or vasculitis (observational, retrospective population-based study)	N	NA	Reference	-	-
		Y	>0 to 4.9 mg/day	0.63 (0.59-0.67)	-	-
		Y	5 to 7.4 mg/day	1.03 (0.98-1.09)	-	-
		Y	≥7.5 mg/day	1.2 (1.16-1.25)	-	-
		Y	GC users all doses	-	2.05 (1.99-2.10)	-
		Every ↑ of 5 mg/day	Current dose per 5 mg/d	1.26 (2.24-1.28)	-	-
Oh et al. 2020[13]	RA, SLE, OA, allergic disease, and others (observational, retrospective study)	Y	GC prescribed regularly and continuously over ≥30 days	1.41 (1.28-1.55)	-	-
		Y	Prednisolone >5 mg/day	1.52 (1.32-1.76)	-	-
		Y	Prednisolone ≤5 mg/day	1.34 (1.18-1.51)	-	-
		N	No GC use or use for less than 30 days	Reference	-	-
Wilson et al. 2017[14]	Giant cell arteritis (observational, case-control study)	N	≤5 mg/day	Reference	-	-
		Y	>5 to ≤10 mg/day	1.1 (0.8-1.5)	-	-
		Y	>10 to ≤20 mg/day	1.4 (1.0-2.0)	-	-
		Y	>20 to ≤30 mg/day	1.7 (1.0-2.8)	-	-
		Y	> 30 mg/day	2.1 (1.3-3.5)	-	-

GC, glucocorticoid; **HR**, hazard ratio; **IBS**, irritable bowel syndrome; **N**, no; **NA**, not available; **OA**, osteoarthritis; **PY**, patient-years; **RA**, rheumatoid arthritis; **RR**, relative risk; **SLE**, systemic lupus erythematosus; **Y**, yes.

RESULTS

Mortality risk in patients taking GCs vs patients not taking GCs

- The highest risk associated with GC use was reported in patients with RA (HR 11, 95% CI: 8.87-13.6)[10]
- Patients treated with GCs for RA had almost 3 times higher mortality rate than those not taking GCs (44.0 [42.1-46.0] vs 15.5 [14.6-16.5]) per 1000 patient-years[10]

Dose-related mortality risk in patients taking GCs vs patients not taking GCs

- At GC doses <5 mg/day, the mortality HR for patients taking GCs vs non-users ranged from 0.63 (0.59-0.67)[12] to 1.84 (1.69-2.00)[5]
- At GC doses ≥10 mg/day, mortality HR ranged from 1.4 (1.0-2.0)[14] to 2.56 (2.35-2.80)[5]
- At GC doses ≥15 mg/day, mortality HR ranged from 2.83 (1.41-5.66)[7] to 11 (8.87-13.6)[10]

Correlations between higher GC dose and higher risk of mortality

- 5-year mortality was higher for patients taking GC doses >5mg/day (HR 1.52, 95% CI: 1.32-1.76) vs those taking GC doses ≤5 mg/day (HR 1.34, 95% CI: 1.18-1.51)[13]
- GC doses ≥10 mg/day was associated with increased mortality (HR 2.56, 95%CI: 2.35-2.80) vs lower GC doses of <5 mg/day (HR 1.84, 95% CI: 1.69-2.00)[5]
- Higher GC doses of >30 mg/day were associated with increased death (HR 2.1, 95% CI: 1.3-3.5, p<0.001) vs ≤5 mg/day[14]

CONCLUSIONS

- **Long-term GC therapy and/or use of higher GC doses increases mortality risk (as much as 3-fold)**
- **The evidence collated in this SLR highlights the importance of minimizing reliance on GCs in managing chronic conditions**

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DISCLOSURES: VR, CVS, TH, and DG are employees of argenx. MS is an employee of Sterias. JHS has served as a consultant to argenx on glucocorticoid toxicity and is the chair of the Scientific Advisory Board at Steritas.
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