Mortality Risk by Functional Status and Health-related Quality of Life in Patients with Rheumatoid Arthritis

KALEB MICHAUD, MONTSERRAT VERA-LLONCH, and GERRY OSTER

ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) are at increased risk of death. Modern RA therapy has been shown to improve health status, but the relationship of such improvements to mortality risk is unknown. We assessed the relationship between health status and all-cause mortality in patients with RA, using the Health Assessment Questionnaire (HAQ) and the Medical Outcomes Study Short Form-36 questionnaire (SF-36) physical and mental component summary scores (PCS, MCS).

Methods. Subjects (n = 10,319) were selected from the National Data Bank for Rheumatic Diseases, a prospective longitudinal observational US study with semiannual assessments of HAQ, PCS, and MCS. Risk of death up to 7 years through 2006 was obtained from the US National Death Index. Relationship of HAQ, PCS, and MCS to mortality was assessed using Cox regression models; prediction accuracy was compared using Harrell's concordance coefficient (C).

Results. Over 64,888 patient-years of followup, there were 1317 deaths. Poorer baseline health status was associated with greater mortality risk. Adjusting for age, sex, and baseline PCS and MCS, declines in PCS and HAQ were associated with higher risk of death. HAQ improvement was associated with reduced mortality risk from 6 months through 3 years; a similar relationship was not observed for PCS or MCS improvement. Controlling for baseline values, change in PCS or HAQ did not improve prediction accuracy.

Conclusion. The HAQ and the SF-36 PCS are similarly and strongly associated with mortality risk in patients with RA. Change in these measures over time does not appear to add to predictive accuracy over baseline levels. (First Release Nov 15 2011; J Rheumatol 2012;39:54–9; doi:10.3899/jrheum.110491)

Key Indexing Terms:
MORTALITY HEALTH STATUS RHEUMATOID ARTHRITIS
SF-36 HEALTH ASSESSMENT QUESTIONNAIRE

Health-related quality of life (HRQOL) is significantly impaired in patients with rheumatoid arthritis (RA) as a result of pain, deficits in physical functioning, and fatigue associated with this disease[1]. The Health Assessment Questionnaire (HAQ) and the Medical Outcomes Study Short Form-36 questionnaire (SF-36) are commonly used measures of patient outcome in RA, and are often used as formal assessment tools in clinical trials of new therapies.

Mortality risk — especially due to cardiovascular disease[2,3] — has been reported to be elevated in patients with RA[4,5,6]. In healthy and older persons with coronary heart disease, arthritis, lung disease, and kidney disease, physical and mental functioning and HRQOL have been reported to be important predictors of death[7,8,9,10,11,12,13,14,15,16]. A few studies have examined whether the HAQ is predictive of mortality in patients with RA[17,18,19], but to our knowledge the predictive ability of the SF-36 has not been examined in this patient population.

We examined whether the HAQ and the SF-36 physical and mental component summary scores (PCS and MCS) are also predictive of mortality in patients with RA, as reported in numerous other patient populations. In addition, we investigated the influence on mortality of specific improvement and worsening in PCS, MCS, and HAQ over a variety of time periods (6 months to 4 years). Knowledge of whether such relationships exist and their quantitative effect could contribute substantially to both epidemiologic and experimental research as well as clinical care.

MATERIALS AND METHODS

Patients in this study were part of the National Data Bank for Rheumatic Diseases (NDB) open-cohort longitudinal observational study of RA outcomes[20,21,22]. Participants are volunteers who are not compensated for their participation. Beginning in 1998, NDB participants were recruited from the practices of US rheumatologists in an ongoing manner and followed prospectively with semiannual, detailed, 28-page questionnaires. In addition to demographics, assessment measures included the Stanford Health Assessment Questionnaire functional disability index (HAQ)[23,24] and the

From the University of Nebraska Medical Center, Omaha, Nebraska; National Data Bank for Rheumatic Diseases (NDB), Wichita, Kansas; Vertex Pharmaceuticals, Cambridge, Massachusetts; and Policy Analysis Inc., Brookline, Massachusetts, USA.

Partial support for this study was provided by Bristol-Myers Squibb.

K. Michaud, PhD, University of Nebraska Medical Center, National Data Bank for Rheumatic Diseases; M. Vera-Llonch, MD, MPH, Vertex Pharmaceuticals; G. Oster, PhD, Policy Analysis Inc.

Address correspondence to K. Michaud, 986270 Nebraska Medical Center, Omaha, NE 68198-6270, USA. E-mail: kmichaud@unmc.edu

Accepted for publication August 19, 2011.

SF-36[25]. Information on mortality for all patients in the NDB is obtained from the US National Death Index[26]; there is roughly a 2-year delay in the reporting of deaths.

The HAQ is a self-administered questionnaire consisting of 20 questions concerning activities of daily living and 21 questions relating to the use of aids and devices and help from others. The range of possible values is from 0 (no functional impairment) to 3 (complete functional impairment) in 0.125 increments. The SF-36 is a self-administered questionnaire that measures 8 domains of HRQOL: physical functioning, role limitations due to physical problems, bodily pain, vitality, social functioning, role limitations due to emotional problems, mental health, and general health perceptions. The SF-36 PCS and MCS scales are constructed by applying published weights to individual domain scores. The mean and SD of the PCS and MCS are both 50 and 10, respectively, in the general US population, and unlike the HAQ scale, an increase in PCS or MCS score corresponds to an improvement in health.

We used questionnaire responses beginning in January 1999 and ending in July 2005, for a total of 14 semiannual assessment periods (7 years). Information on mortality was current through 2006; patients were censored as to vital status as of December 31, 2006. Patients were required to have at least 2 completed PCS/MCS assessments for inclusion in the study, the earliest of which was designated the "baseline" observation. Patients aged < 18 years, as well as those who entered the NDB as part of an NDB-conducted drug safety registry, were excluded in order to have a more representative RA study sample and a more homogeneous recruitment method[22].

We examined whether baseline values of the PCS, MCS, and the HAQ were predictive of mortality. We also examined how the changes in these scores from baseline at 6 months, 1 year, 2 years, 3 years, and 4 years, respectively, were predictive of mortality. In analyses of baseline values, PCS and MCS scores were stratified following SD widths[10] and visual inspection of the data as follows: ≤ 20, 21–30, 31–40, 41–50, and ≥ 50. Values of the HAQ at baseline were similarly stratified by visual inspection as follows: 0.0, 0.1–0.4, 0.5–0.9, 1.0–1.4, 1.5–1.9, 2.0–2.4, and 2.5–3.0.

In analyses of change scores, responses were also stratified following visual inspection of the data. For the PCS and MCS, change scores from baseline between –4 and +4 were designated "no change"; corresponding values for the HAQ were –0.125 to +0.125. These values or at least the width of the categories are generally accepted as greater than or equal to the minimal clinically important differences for these measures[25]. We also examined the predictive ability of the PCS, MCS, and HAQ as continuous variables; changes in mortality risk were estimated for each 5-unit decrement (i.e., worsening) in the PCS and MCS, and for 0.25-unit increases (worsening) of the HAQ.

Statistical analyses. We used Cox regression to examine the relationship between PCS, MCS, and HAQ change scores and mortality. Entry to survival models was at the baseline observation and continued until either date of death or censorship at their last observation. Except as otherwise indicated in the Results section, covariates in these models included age, sex, and baseline PCS and MCS. The reference categories in the Cox regression were the "no change" patients (i.e., –4 to 4 for both the PCS and MCS, and –0.125 to 0.125 for the HAQ). In Cox regressions examining the predictive value of baseline scores, the reference categories were ≥ 50 for the PCS and MCS, and 0.0 for the HAQ. Harrell's C statistic was used to assess the predictive value of the measures of interest, defined as the proportion of all subject pairs in which the predictions and outcomes were concordant[28].

There were 2 types of missing data in the study sample: missing variables and missing observations. At the patient level, a variable was missing for a given observation when the SF-36 and HAQ were part of the patient questionnaire, but the patient did not complete a sufficient number of items to permit valid scoring. The percentage of observations with missing variables was 4.7% for the PCS and MCS and 1.1% for the HAQ. The HAQ was missing for 0.7% of valid PCS/MCS assessments. Missing observations occurred when patients did not complete 1 or more semiannual questionnaires (9.7% of observations) or requested a shorter questionnaire that did not contain the PCS/MCS (2.5% of observations) during 6-month periods between non-missing observations. Overall, 64.8% of study subjects had no missing observations, 21.6% had 1 missing observation, 7.7% had 2 missing observations, 3.5% had 3 missing observations, and 2.3% had 4 or more missing observations. We replaced all missing data using multiple imputation by chained equations to create multiple imputed datasets for analyses[29], and we combined data according to Rubin's rules[30]; prior analyses done similarly are described elsewhere[31]. Data were analyzed using Stata, version 10.1 (Stata C; release 10.0; 2007. Stata Corp., College Station, TX, USA). All tests were 2-tailed and a significance level of 0.05 was used.

RESULTS

After excluding 3220 patients with RA for not having 2 SF-36 observations, a total of 10,319 patients remained eligible for study. The mean age of subjects at entry into the NDB was 59.0 (SD 13.1) years; the mean duration of RA at entry was 12.8 (SD 11.1) years (Table 1). At study entry, the mean value of the HAQ was 1.01 (SD 0.71); corresponding scores for the PCS and MCS were 36.5 (SD 11.0) and 49.7 (SD 11.1), respectively.

Mortality in relation to baseline values of PCS, MCS, HAQ. Risks of mortality associated with various levels of the PCS, MCS, and HAQ are reported in Table 2. Poorer baseline health status, as indicated in all 3 measures, was associated with higher mortality risk. In the PCS category that encompassed the mean value for this measure[31,32,33,34,35,36,37,38,39], the hazard ratio (HR) for death was 2.0 compared to the ≥ 50 category, and in the corresponding HAQ category (1.0–1.4) the HR was 1.8 compared to the 0.0 category. When we considered continuous predictor variables, a

Table 1. Characteristics of 10,319 patients with RA at baseline. Data are mean (SD) unless otherwise indicated.

Variable	
Age, yrs	59.0 (13.1)
Male, %	22.8
Education level, yrs, %	13.5
0-8	2.3
8-11	7.2
12	35.8
13-15	26.5
≥ 16	28.2
Ethnic origin, %	
White, not of hispanic origin	91.6
Black, not of hispanic origin	3.8
Asian or Pacific Islander	1.0
American Indian or Alaskan native	0.9
Hispanic	2.4
Other	0.5
RA duration, yrs	12.8 (11.1)
Baseline PCS	36.5 (11.0)
Baseline MCS	49.7 (11.1)
Baseline HAQ	1.01 (0.71)
No. deaths	1317

PCS: SF-36 physical component summary; MCS: SF-36 mental component summary; HAQ: Health Assessment Questionnaire-Disability Index; RA: rheumatoid arthritis.

Table 2. Age- and sex-adjusted risk of mortality in patients with RA according to baseline PCS, MCS, and HAQ. N = 10,319 patients, 1317 deaths, and 64,888 patient-years of observation.

Variable	Category	% in Category	HR (95% CI)	p
PCS	≥ 50	14.5	1.0 (referent)	
	41–50	22.6	1.6 (1.2, 2.1)	< 0.001
	31–40	30.6	2.0 (1.6, 2.6)	< 0.001
	21–30	27.3	3.1 (2.5, 4.0)	< 0.001
	≤ 20	5.1	4.9 (3.6, 6.4)	< 0.001
MCS	≥ 50	57.2	1.0 (referent)	
	41–50	21.4	1.4 (1.2, 1.6)	< 0.001
	31–40	15.2	1.7 (1.5, 2.0)	< 0.001
	21–30	5.5	2.0 (1.5, 2.5)	< 0.001
	≤ 20	0.7	1.6 (0.6, 3.8)	0.304
HAQ	0.00	12.3	1.0 (referent)	
	0.125–0.375	14.8	1.4 (1.1, 1.8)	0.010
	0.500–0.875	25.7	1.5 (1.2, 1.9)	0.002
	1.000–1.375	22.3	1.8 (1.4, 2.2)	< 0.001
	1.500–1.875	17.2	2.7 (2.2, 3.5)	< 0.001
	2.000–2.375	6.4	4.0 (3.1, 5.2)	< 0.001
	2.500–3.000	1.3	5.5 (3.9, 7.7)	< 0.001

PCS: SF-36 physical component summary score; MCS: SF-36 mental component summary score; HAQ: Health Assessment Questionnaire-Disability Index; RA: rheumatoid arthritis.

5-unit decline in the PCS was associated with an HR of 1.2 (95% CI 1.2, 1.3); a 5-unit decline in the MCS, an HR of 1.1 (95% CI 1.1, 1.1); and a 1-unit increase in the HAQ, an HR of 1.8 (95% CI 1.7, 1.9).

In Cox regression models controlling for age and sex, the C statistic for the PCS, MCS, and HAQ was 0.77, 0.76, and 0.77, respectively. Because age and sex may contribute substantially to C, we reran the analyses after dropping these 2 variables from the models. The resulting values for the C statistic were 0.63, 0.53, and 0.61 for the PCS, MCS, and HAQ. These results indicate that the MCS has almost no predictive power as it approaches 0.5 (no information), and that the predictive power of the PCS and HAQ are similar, with a slight advantage using PCS.

Mortality in relation to change in PCS, MCS, and HAQ. Risks of death in relation to change in the PCS, MCS, and HAQ over 6 months, 1 year, 2 years, 3 years, and 4 years, adjusting for baseline values of age, sex, PCS, and MCS, are reported in Table 3.

Declines in the PCS of 5–14 units were associated with increased mortality risk at 6 months, 2 years, and 3 years; 15–29 units, increased mortality risk from 1–4 years; and ≥ 30 units, increased risk at 1 and 2 years. HAQ worsening of ≥ 0.5 unit was always associated with increased mortality risk. Except for 2 values, declines in the MCS were not associated with mortality risk.

While HAQ improvement ≥ 0.5 unit was associated with a reduction in mortality risk over all time periods from 6 months through 3 years, improvements in the PCS or MCS were not associated with a decline in mortality risk in any of the time periods we examined (except ≥ 15-unit improvement in the PCS at 1 year). We used Harrell's C to compare change analyses at 1 year. The C statistic for baseline PCS and MCS was 0.63. When PCS, MCS, and HAQ change were added to the model, the C statistics increased to 0.65, 0.63, and 0.64, respectively.

DISCUSSION

Increasingly effective treatments have led to improvements in health status in patients with RA. Among patients in clinical trials, 20% improvements in the PCS and HAQ are common, and many patients achieve 50% or 70% improvements. The PCS has been shown to be a significant predictor of mortality in a number of disease areas, and the HAQ has been shown to be a predictor of mortality in RA[7,8,32,33,34,35,36,37]. It is therefore of considerable clinical interest to know whether changes in health status as measured by the HAQ and the SF-36 are predictive of mortality risk in RA. Not only would this be of clinical interest, but it also would aid in better understanding of the cost-effectiveness of new therapies for RA[38,39,40,41,42].

In 2008, Kroenke, *et al* used data from the Nurses Health Study (NHS) to examine the effect of changes in PCS and MCS on mortality in 40,337 healthy women, aged 46–71 years in 1992[16]. They reported that over a 4-year period, a decline in the PCS > 20 units was associated with a relative risk (RR) of mortality of 3.3; a 10–19 unit decline, an RR of 1.4; and a 5–9 unit decline, an RR of 1.4 — a pattern similar to that observed in our study (Table 3). Improvement of 6–75 units was associated with an RR of 0.72. Although we did not observe a corresponding significant reduction in risk of death with improvement in the PCS, this could simply reflect that few patients in our study population experienced clinically important positive change in this measure. Also,

Table 3. Effect of change from baseline in PCS, MCS, and HAQ scores on mortality in RA over 4 years. PCS analyses adjusted for baseline values of age, sex, PCS, and MCS. MCS analyses adjusted for baseline values of age, sex, PCS, and MCS. HAQ analyses adjusted for baseline values of age, sex, PCS, and MCS. –4 to +4 is considered "no change for PCS and MCS". –0.125 to +0.125 is considered no change for HAQ.

Variable	6 month	Year 1	Year 2	Year 3	Year 4
Patients, no.	10,319	9092	6774	5310	4265
Deaths	1317	1097	724	459	303
Patient-years	64,888	58,900	46,772	38,077	31,571
PCS change, HR (95% CI)					
≤ –30	—*	9.11 (1.27, 65.37)	—*	12.94 (1.79, 93.80)	—*
–15 to –29	1.53 (0.95, 2.49)	2.07 (1.38, 3.12)	2.72 (1.79, 4.15)	2.13 (1.30, 3.50)	2.59 (1.56, 4.28)
–5 to –14	1.20 (1.02, 1.41)	1.12 (0.94, 1.34)	1.55 (1.28, 1.87)	1.33 (1.05, 1.69)	1.18 (0.88, 1.59)
–4 to 4 (referent)	1.00	1.00	1.00	1.00	1.00
+5 to +14	0.92 (0.80, 1.07)	0.87 (0.75, 1.02)	0.92 (0.75, 1.13)	0.92 (0.71, 1.20)	0.92 (0.68, 1.25)
+15 to +30	0.77 (0.50, 1.19)	0.54 (0.30, 0.96)	0.70 (0.42, 1.15)	0.56 (0.30, 1.05)	0.67 (0.31, 1.44)
> +30	—*	—*	—*	—*	—*
Continuous (5-unit PCS decrease)	1.19 (1.05, 1.15)	1.13 (1.08, 1.19)	1.16 (1.10, 1.23)	1.17 (1.09, 1.25)	1.65 (1.08, 1.26)
MCS change HR (95% CI)					
≤ –30	1.48 (0.55, 3.98)	0.49 (0.07, 3.47)	1.35 (0.20, 8.97)	2.05 (0.50, 8.42)	2.96 (0.72, 12.15)
–15 to –29	1.15 (0.89, 1.50)	1.41 (1.10, 1.81)	1.20 (0.87, 1.67)	0.86 (0.55, 1.34)	1.52 (0.98, 2.34)
–5 to –14	0.98 (0.84, 1.14)	1.05 (0.89, 1.23)	1.23 (1.01, 1.50)	1.04 (0.80, 1.35)	1.16 (0.85, 1.59)
–4 to 4 (referent)	1.00	1.00	1.00	1.00	1.00
+5 to +14	0.96 (0.82, 1.12)	0.95 (0.79, 1.14)	1.11 (0.90, 1.36)	0.88 (0.67, 1.15)	1.02 (0.73, 1.42)
+ 15 to +30	1.15 (0.88, 1.49)	1.04 (0.78, 1.38)	1.13 (0.80, 1.58)	0.68 (0.41, 1.12)	0.74 (0.41, 1.34)
> +30	1.43 (0.46, 4.48)	1.54 (0.57, 4.17)	—*	0.72 (0.10, 5.20)	1.65 (0.39, 7.03)
Continuous (5-unit MCS decrease)	1.00 (0.97, 1.04)	1.03 (1.00, 1.07)	1.02 (0.98, 1.07)	1.05 (1.00, 1.10)	1.08 (1.00, 1.05)
HAQ change HR (95% CI)					
≥ 0.500	0.81 (0.68, 0.96)	0.80 (0.66, 0.97)	0.78 (0.62, 1.00)	0.70 (0.51, 0.96)	0.87 (0.60, 1.26)
+0.250 to +0.375	0.93 (0.77, 1.12)	1.09 (0.89, 1.34)	0.98 (0.75, 1.29)	1.03 (0.73, 1.47)	0.99 (0.63, 1.57)
–0.125 to +0.125 (referent)	1.00	1.00	1.00	1.00	1.00
< –0.375 to –0.250	1.00 (0.83, 1.22)	1.32 (1.08, 1.61)	1.06 (0.82, 1.38)	1.29 (0.95, 1.77)	1.42 (0.96, 2.09)
< –0.500	1.31 (1.11, 1.54)	1.44 (1.22, 1.70)	1.54 (1.28, 1.85)	1.58 (1.26, 1.99)	1.63 (1.23, 2.15)
Continuous (0.25-unit HAQ increase)	1.12 (1.08, 1.17)	1.16 (1.11, 1.21)	1.16 (1.10, 1.21)	1.21 (1.14, 1.28)	1.19 (1.11, 1.27)

* HR is not estimable. PCS: SF-36 physical component summary score; MCS: SF-36 mental component summary score; HAQ: Health Assessment Questionnaire-Disability Index; HR: hazard ratio.

the study population in the NHS was substantially different from ours, in that it was not limited to patients with RA and excluded more than 10,000 subjects with serious illnesses. Although the authors do not provide baseline PCS and MCS scores for the study population, the health status of that population was certainly better than that of our cohort of patients with RA.

In a second clinical study of 7702 participants receiving ambulatory care at a Veterans Affairs (VA) facility, Fan, *et al* examined the relationship between 1-year mortality risk and change in the PCS over the prior year[13]. After adjusting for baseline PCS and comorbidity, a 10-point decrease in PCS was found to be associated with an increased risk of death (OR 2.3, 95% CI 1.6–3.4). However, as with our study, the addition of change scores improved prediction accuracy only slightly compared with baseline PCS alone (area under the curve 0.64 vs 0.62).

We investigated the association between health status — at baseline and changes over time — and mortality in patients with longstanding RA. We found that changes in the PCS and HAQ did not contribute substantially to predictive value over and above the baseline values of these variables, as evidenced by minimal changes in Harrell's C. Stated differently, the starting level of the PCS and HAQ are more important than the magnitude of change in these measures.

Second, we found that the predictive ability of the PCS and HAQ are almost the same, and that these measures can provide important and clinically useful information to clinicians and trialists. For example, a HAQ score of 1.0 indicates a mortality risk of 1.8 compared with a patient with RA in remission (HAQ score of 0.0) or a person without functional limitations. Similarly, a HAQ score of 1.5, which is common among patients participating in clinical trials, is associated with a mortality risk of 2.7 compared with persons without functional limitations. We note that while the PCS and HAQ provide almost equivalent information, the HAQ may be preferred to the PCS as it can be administered in the clinic and scored in seconds.

With respect to change in the PCS and HAQ, improvement was less often and less strongly associated with a decrease in the risk of mortality compared with the association between declines in these measures and an increased risk of death. In addition, the association between HAQ improvement and mortality was stronger than the associa-

tion between PCS improvement and mortality. One possible reason for this finding was that the multiple scales used in the PCS may buffer change compared with the unidimensional HAQ.

We urge caution in extrapolating our findings, which are based on data collected semiannually and without respect to disease flare, to the clinical trial setting. Patients in clinical trials may be selected for inclusion because of flare, and may manifest dramatic placebo effects. In some circumstances, health status may appear worse than it is, and response may appear to be better than it would be in a practice setting[43].

The PCS and HAQ are about equal in their prediction of mortality risk. The HAQ is strongly associated with mortality risk in patients with RA and can be estimated simply in the clinic. The predictive ability of the PCS in RA corresponds to results demonstrated in other disease areas. Although changes in the PCS and HAQ over time correlate with mortality risk, they do not appear to provide substantive additional information beyond the absolute values of these measures. The relationship of these patient-reported measures of functional and health status with longer-term health outcomes can be useful in both clinical and research settings, with the ultimate goal of improving patient care.

ACKNOWLEDGMENT

The authors are indebted to Dr. Frederick Wolfe, who aided in the statistical analyses and helped with some of the text.

REFERENCES

1. Strand V, Khanna D. The impact of rheumatoid arthritis and treatment on patients' lives. Clin Exp Rheumatol 2010;28 Suppl 59:S32-40.
2. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. Am J Med 2008;121 Suppl 1:S9-14.
3. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. Arthritis Rheum 2008;59:1690-7.
4. Naz SM, Symmons DP. Mortality in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007;21:871-83.
5. Gonzalez A, Maradit Kremers H, Crowson CS, Nicola PJ, Davis JM 3rd, Therneau TM, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56:3583-7.
6. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 2007;46:350-7.
7. Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, et al. Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int 2003;64:339-49.
8. Sprenkle MD, Niewoehner DE, Nelson DB, Nichol KL. The Veterans Short Form 36 questionnaire is predictive of mortality and health-care utilization in a population of veterans with a self-reported diagnosis of asthma or COPD. Chest 2004;126:81-9.
9. Singh JA, Nelson DB, Fink HA, Nichol KL. Health-related quality of life predicts future health care utilization and mortality in veterans with self-reported physician-diagnosed arthritis: The Veterans Arthritis Quality of Life Study. Semin Arthritis Rheum 2005; 34:755-65.
10. Rumsfeld JS, Mawhinney S, McCarthy M Jr, Shroyer AL, Villanueva CB, O'Brien M, et al. Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. Participants of the Department of Veterans Affairs Cooperative Study Group on Processes, Structures, and Outcomes of Care in Cardiac Surgery. JAMA 1999;281:1298-303.
11. Lee Y. The predictive value of self assessed general, physical, and mental health on functional decline and mortality in older adults. J Epidemiol Community Health 2000;54:123-9.
12. Dominick KL, Ahern FM, Gold CH, Heller DA. Relationship of health-related quality of life to health care utilization and mortality among older adults. Aging Clin Exp Res 2002;14:499-508.
13. Fan VS, Au DH, McDonell MB, Fihn SD. Intraindividual change in SF-36 in ambulatory clinic primary care patients predicted mortality and hospitalizations. J Clin Epidemiol 2004;57:277-83.
14. Dorr DA, Jones SS, Burns L, Donnelly SM, Brunker CP, Wilcox A, et al. Use of health-related, quality-of-life metrics to predict mortality and hospitalizations in community-dwelling seniors. J Am Geriatr Soc 2006;54:667-73.
15. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295:801-8.
16. Kroenke CH, Kubzansky LD, Adler N, Kawachi I. Prospective change in health-related quality of life and subsequent mortality among middle-aged and older women. Am J Public Health 2008;98:2085-91.
17. Yelin E, Trupin L, Wong B, Rush S. The impact of functional status and change in functional status on mortality over 18 years among persons with rheumatoid arthritis. J Rheumatol 2002;29:1851-7.
18. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum 2003;48:1530-42.
19. Jacobsson LT, Turesson C, Nilsson JA, Petersson IF, Lindqvist E, Saxne T, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:670-5.
20. Wolfe F, Michaud K. A brief introduction to the National Data Bank for Rheumatic Diseases. Clin Exp Rheumatol 2005;23:S168-S71.
21. Nadareishvili Z, Michaud K, Hallenbeck JM, Wolfe F. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: A nested, case-control study. Arthritis Rheum 2008;59:1090-6.
22. Wolfe F, Michaud K. The National Data Bank for Rheumatic Diseases: A multi-registry rheumatic disease data bank. Rheumatology 2011;50:16-24.
23. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
24. Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum 2000;43:2751-61.
25. Stewart AL, Hays RD, Ware JE. The MOS Short-form General Health Survey. Med Care 1988;26:724-35.
26. Curb JD, Ford CE, Pressel S, Palmer M, Babcock C, Hawkins CM. Ascertainment of vital status through the National Death Index and the Social Security Administration. Am J Epidemiol 1985; 121:754-66.
27. Wolfe F, Michaud K, Strand V. Expanding the definition of clinical differences: From minimally clinically important differences to really important differences. Analyses in 8931 patients with rheumatoid arthritis. J Rheumatol 2005;32:583-9.
28. Harrell FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med 1984;3:143-52.
29. Royston P. Multiple imputation of missing values. Stata J 2004;4:227-41.
30. Rubin DB. Multiple imputation for non-response in surveys. New

York: J. Wiley & Sons; 1987.
31. Wolfe F, Michaud K. The loss of health status in rheumatoid arthritis and the effect of biologic therapy: A longitudinal observational study. Arthritis Res Ther 2010;12:R35.
32. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav 1997;38:21-37.
33. Farragher TM, Lunt M, Bunn DK, Silman AJ, Symmons DP. Early functional disability predicts both all-cause and cardiovascular mortality in people with inflammatory polyarthritis: Results from the Norfolk Arthritis Register. Ann Rheum Dis 2007;66:486-92.
34. Singh JA, Nelson DB, Fink HA, Nichol KL. Health-related quality of life predicts future health care utilization and mortality in veterans with self-reported physician-diagnosed arthritis: The Veterans Arthritis Quality of Life Study. Semin Arthritis Rheum 2005; 34:755-65.
35. Sokka T, Hakkinen A, Krishnan E, Hannonen P. Similar prediction of mortality by the Health Assessment Questionnaire in patients with rheumatoid arthritis and the general population. Ann Rheum Dis 2004;63:494-7.
36. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum 2003;48:1530-42.
37. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously — predictive markers, socioeconomic status and comorbidity [editorial]. J Rheumatol 1986;13:841-5.
38. Dreiher J, Ginsberg G, Rabinowitz G, Raskin-Segal A, Weitzman R, Porath A. Estimation of mortality savings due to a national program for diabetes care. Eur J Intern Med 2009;20:307-12.
39. Goldbach-Mansky R, Lipsky PE. New concepts in the treatment of rheumatoid arthritis. Annu Rev Med 2003;54:197-216.
40. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: A review. Rheumatology 2004;43:267-71.
41. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. J Rheumatol 2008;35:1745-53.
42. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology 2008;47:535-41.
43. Wolfe F, Michaud K. Towards an epidemiology of rheumatoid arthritis outcome with respect to treatment: Randomized controlled trials overestimate treatment response and effectiveness. Rheumatology 2005;44 Suppl 4:iv18-iv22.