Multimorbidity Index as a Tool for Projection of Health and Mortality among US Older Adults: Medicare-based analysis

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Introduction

Older persons constitute the fastest growing sector of the U.S. population. They often have several chronic diseases; such multimorbidity merits special attention due to rising costs of medical services and long-term care. To address an impending crisis for US policymakers, financial planners, and medical services involved in the Medicare program, we need tools better able to capture multimorbidity effects. Such tools would allow for more precise predictions of future mortality and health trends in the medically complex U.S. elderly population. During recent decades, the concept of comorbidity has been changing, with an increasing focus on multimorbidity and its effects in epidemiological studies results, health services planning, and clinical care (McCormick, Boling, 2005; Valderas et al., 2009; Parekh, Barton, 2010; Boyd et al., 2005, 2010).

Although numerous indices have been used in health studies, no "gold standard" for measuring multimorbidity has been established yet. The most frequently applied, the Charlson comorbidity index (CCI) in its original version (developed in 1987, Charlson et al., 1987) reflects the contributions of different diseases to the risk of non-disease-specific death. It became a "comorbidity" index in precise meaning of this term (i.e., when one specific disease was selected as a main point of interest) later after being used in multiple clinical studies to estimate the risk of deaths among patients with the disease of interest. However, since the mid-1980s when the CCI was developed, many active screening strategies and new approaches to cancer treatment (e.g., for prostate, breast, and cervical cancers*)* have been introduced. Also, changes in prevention strategies and achievement in treatment of cardio- and cerebrovascular diseases have changed the role of many diseases as contributors to mortality, especially for the US elderly population. When evaluating multimorbidity in this population, the severity of diseases that are common at these ages should be taken into account. An overestimation of conditions heavily weighted in CCI (such as AIDS which is still more prevalent among young and middle-aged patients than among the elderly patients) and underestimation of some highly prevalent conditions (such as heart failure and Alzheimer's disease) should be avoided. Also, existing multimorbidity indices have never been validated using the national-scale administrative Medicare-based data. To our best knowledge, Medicare-based datasets used in this study are capable of providing more detailed information than those used in published studies, to construct a multimorbidity index with higher power to predict mortality and other outcomes. Thus, the rationale for this study is the lack of a high-precision tool for the prediction of health status and mortality of older persons. New opportunities opened by the availability of large-scale Medicare-based information are very useful in providing the national level data for developing such a tool.

Data and Methods

Two Medicare-linked datasets, the National Long Term care Survey (NLTCS-Medicare) and the Surveillance, Epidemiology and End Results (SEER-Medicare) were used in the analysis. They contain information from the Medicare files of service use beginning from 1991. All individuals in the SEER-Medicare and NLTCS-Medicare are longitudinally tracked for Medicare Part A and Part B service use. The records are available for each institutional (inpatient (INP), outpatient (OTP),

skilled nursing facility (SNF), hospice (HSP), or home health agency (HHA)) and non-institutional (Carrier-Physician-Supplier (CAR) and durable medical equipment (DME) providers) claim types.

Two of the six NLTCS waves, namely cohorts of 1994 and 1999 were chosen for analysis primarily because the high quality Medicare follow-up data are available only since 1991 and the complete 5-year follow-up after the NLTCS interview is accessible only for these two waves after 1991. The NLTCS uses a sample of individuals drawn from the national Medicare enrollment files. In total, 34,077 individuals were followed-up for 5 years. So-called "screener weights" released with the NLTCS were used in this study to produce the national population estimates.

The collection of SEER data began in 1973 and currently covers about 26% of the U.S population. The SEER-M dataset includes Medicare records for individuals with diagnosed breast (the number of patients, n=353,285), colon (n=222,659), lung (n=342,961), prostate (n=448,410) cancers and skin melanoma (n=101,123), as well as Medicare records for 5% control. In total, Medicare records for 2,154,598 individuals are available in SEER-Medicare.

In addition, we used the Multiple Cause of Death data to perform a specific analysis, i.e., to identify the diseases which appeared in death certificates with high frequency and therefore potentially would contribute to the newly constructed multimorbidity index.

Adjusted Multimorbidity Index

The **A**djusted to the US elderly population **M**ulti**M**orbidity **I**ndex (AMMI) was calculated in terms of disease-specific weights, w_d , through the sum over all contributed diseases as

$$C(t) = \sum_d w_d I_d(t) . \quad (1)$$

The term $I_d(t)$ indicates the presence of d*th* condition in the considered individual, i.e., $I_d(t) = 1$ if the individual has the condition and $I_d(t) = 0$ if not. These weights are defined considering the effect of individual diseases on mortality rate. To use the AMMI as a characteristic of individual health in predictive models we need to evaluate the AMMI at any time of individual follow-up. The calculation of the AMMI using administrative data requires certain specifications to clarify: i) how to optimally specify the list of contributing diseases, ii) how to individualize disease prevalence $I_d(t)$ in any time t of individual follow-up, and iii) how to calculate disease-specific weights w_d .

Results

Evaluation of AMMI

The list of the conditions that contributed to the AMMI was identified by incorporating information about i) the frequency of diseases appearing in death certificates available in the Multiple Cause of death data, ii) the strength of association between the prevalence of specific disease/disease clusters and mortality in Medicare based datasets, and iii) diseases that contribute to the Charlson comorbidity index and several other comorbidity indices.

We analyzed data on multiple cause of death occurring at 65+ in 1996-1998. These years were chosen because i) 1998 is the last when the ICD-9 coding system was used, and ii) 1996-1998 are in the middle of the time period we analyze in this paper (1991-2005). First, we considered the primary grouping of diseases in the ICD-9 (17 groups) and calculated the frequencies of diseases taking into account only underlying causes of death. We found the most deaths in our data were due to i) diseases of the circulatory system (390-459): 46.3%, ii) neoplasms (140-239): 22.5%, iii) diseases of the respiratory system (460-519): 11.6%, iv) endocrine, nutritional and metabolic diseases, and immunity disorders (240-279): 3.69%, and v)

diseases of the digestive and renal systems (520-579): 3.04%. Second, we analyzed frequencies of three-digit codes in underlying cause of death. One unexpected finding is the high frequencies for "unspecified disease". The 6 top (with frequencies above 4%) are: 414–Other forms of chronic ischemic heart disease (12.95%), 410–Acute myocardial infarction (9.77%), 162–Malignant neoplasm of trachea, bronchus, and lung (6.29%), 436–Acute, but ill-defined, cerebrovascular disease (4.93%), 496–Chronic airway obstruction, not elsewhere classified (4.22%), and 486–Pneumonia, organism unspecified (4.04%).
Third, we analyzed frequencies of secondary causes for the most important underlying causes of death.

Based on these analyses as well as on Charlson's original selection plus accounting for the changes in disease incidence and mortality structure in the US elderly since the late 1980s, the diseases of cardiovascular, cerebrovascular, pulmonary, neurologic, metabolic, renal, gastrointestinal, and musculoskeletal systems, as well as cancers, anemia, depression, HIV/AIDS, obesity/weight deficiency, and tobacco, alcohol, and prescribed medicine abuses were included in the analysis. Table 1 provides ICD-9 codes for selected diseases or disease clusters.

Even when the list of contributing diseases is fixed, the calculation of the comorbidity and AMMIs using the eq. (1) still requires addressing certain issues: i) how to individualize disease prevalence $I_d(t)$ in any time t of individual follow-up, and ii) how to calculate disease-specific weights w_d.

The estimation of individual disease presence from Medicare records requires the elaboration of specific criteria indicating that an individual has a disease at any time t of his/her follow-up. For the task of comorbidity evaluation, estimating prevalence of comorbid disease is required for time of main diagnosis only. Typically a time period of one year is used for the search of ICD codes for comorbid diseases. In the case of multimorbidity, whole after-65-life time trajectories for all contributed diseases have to be constructed. Three criteria need to be elaborated in order to estimate individualize disease prevalence $I_d(t)$ at any time t of individual follow-up. First, optimal disease-specific time periods (τ_d) before the time point of interest (t) (how long since last visit individual still had the condition) were evaluated. Second, since an individual history contains 7 Medicare sources of information, the question is which of them (or maybe all of them) should be used in the definition. For example, in the definition of incidence rate calculated using Medicare histories four base sources (INP, OTP, CAR, SNF) are used (Akushevich et al., 2012a,b; 2013a). Third, since each claim in Medicare records can be base or secondary, the decision about using secondary cases also has to be made. Specifying these three items results in the representation of individual prevalence in the form of the indicator function $I_d(t)$. The best model was identified by the analysis of association with mortality according to the likelihood-ratio test and AIC. The analysis showed that the optimal strategy is that all codes (both base and secondary) and base Medicare sources (INP, OTP, SNF, and CAR) should be used. Comparison of the effects given by all models with different options is the subject of sensitivity analyses.

As in the majority of approaches for construction of co- and multimorbidity indices, disease-specific weights w_i were estimated through rounded logarithms of hazard ratios of respective conditions on mortality. The Cox proportional model with multivariate time-dependent predictions (i.e., disease prevalence) is used to estimate these weights. This computation requires evaluation of disease prevalence at all times of individual follow-up, therefore we use different assumptions about the Medicare sources, disease-specific times τ_d, primary/secondary codes discussed above. The best model is identified according to the likelihood-ratio test and/or AIC. The disease specific weights for diseases defined in Table 1 estimated using the SEER-Medicare dataset are shown in Table 2.

Using a similar approach we also re-estimated the weights from the original CCI using the Medicare data for time period 1991-2005 with the Cox proportional model with multivariate time-dependent predictions (i.e., disease presence $I_d(t)$). Compared with the original CCI, some diseases (such as heart failure, myocardial infarction, stroke, respiratory diseases, dementia) had higher weights for the current elderly population, while the weights of other diseases (such as renal failure, chronic liver diseases, HIV/AIDS, carcinoma in situ, solid cancers with effective screening) were lower than in the original CCI which was estimated for the full population in the mid-1980s.

Analysis and Modeling Using AMMI and its Validation.

Three steps of the analyses included: i) an empirical analysis of the AMMI and comparison of CCI and AMMI, ii) mortality and dynamic model development, and iii) a validation study.

Empirical analysis. Formula (1) is used to evaluate the AMMI for each time point of individual follow-up. Figure 1 presents the distributions of the AMMI evaluated for the pooled NLTCS-Medicare cohort. Means for the various population groups and standard deviations are also presented. They show that there is no difference between males and females, the white population is healthier than the non-white, and as expected, the mean for advanced ages is much higher then for younger adults. Figure 3 shows the dynamics of changes of the AMMI with time. Note, that an increase in AMMI with time is observed not only for the NLTCS-Medicare cohorts (expected because time dynamics simply reflect aging of cohorts), but also for the SEER-Medicare estimate that is designed to reflect estimates in the general population every year.

Then we evaluated empirical plots of the CCI and AMMI. Several basic properties of the index were evaluated: i) the age pattern of the index; ii) sex-, race, cohort-, and period-effects, and iii) the association between the shape of the AMMI (i.e., slope or curvature) and mortality (see Figure 3). When the same analysis was performed for CCI, it showed that CCI, over periods and cohorts, did not completely reflect the respective plots for mortality - that was one of the motivations for developing the AMMI.

Modeling. There are two specific models have to be developed to predict mortality for a cohort of older adults. The first is the mortality model, i.e., the model that predicts mortality in terms of current AMMI, history of its measurements, and other covariates. The second is the dynamic model for AMMI changes, i.e., the model that predicts future values of AMMI using similar predictors. The mortality model was chosen in the form:

$$logit(Prob(death = 1 \mid C_0, C_3, Age, Y_b)) = u + \beta_0 C_0 + \beta_1 C_3 + \beta_{Age}(Age - 70) + \beta_b(Y_b - 1930) \quad (2)$$

Justification for this model selection is as follows. C_0, the multimorbidity index in the last month, is the major predictor of mortality. Its effect is linear that results in exponential relation of mortality and C_0. The exponential relation is expected because C_0 is constructed by HR evaluating using the Cox proportional hazard model. This shape of relation between mortality and the AMMI was also confirmed by two separate analyses. The first was based on the model with categorical AMMI. Estimates of the effects of different categories were close to linear thus confirming (2). The second used individual disease prevalence $I_d(t)$ as predictors. Estimates of the effects of specific diseases were close to estimated weights estimated using the Cox model.

The second predictor standing in (2), C_3, is the multimorbidity index measured three

months before the current month. Occurrence of the term reflecting previous values of the index is important because it allows for capturing the effect of increasing multimorbidity before death. The effect of age is linear corresponding to the gamma-Gompertz model of mortality. The parameter Y_b reflects the cohort effect. The linear form for this effect is justified by preliminary modeling results with the categorical cohort index. The estimated pattern was close to linear.

The Dynamic Model for AMMI was selected in the form

$$\Delta_{01} = C_0 - C_1 = u + \beta_1 C_1 + \beta_\Delta \Delta_{13} + \beta_{Age}(Age - 70) + \beta_b(Y_b - 1930) \quad (3)$$

with the same notation as in (2). What is new here is i) the outcome variable: difference between AMMIs measured in the current and last months and ii) one of the predictors: difference between AMMIs measured in previous months ($\Delta_C = C_1 - C_3$). Similarly to the analysis with mortality models we compared parameter estimates with an alternative, more sophisticated, model and found consistency in model parameter estimates. The model is known as the proportional-odds model and specified as

$$logit(Prob(\Delta I_C = k \mid I_{C1}, \Delta_{13}, Age, Y_b)) = u_k + \beta_1 I_{C1} + \beta_\Delta \Delta_{13} + \beta_{Age}(Age - 70) + \beta_b(Y_b - 1930) \quad (4)$$

Both outcome (ΔI_C) and main predictor (I_{C1}) are rounded Δ_{01} and C_1 to integers. The model is estimated for each level of I_C separately. Because of multiple levels of the outcome, the model has multiple intercepts.

Parameter estimates for models (2) and (3) are given in Table 3. Excellent agreement between parameters estimated for both datasets is found. The odds ratio of the current AMMI (i.e., C_0) is 1.53 (exponent of the parameter estimates presented in Table 3) per one unit of the index. As expected the estimate of the AMMI measured earlier is negative (i.e., odds ratio is lower than one). This reflects the effect of increasing multimorbidity before death. The effect of age is at the level usually estimated for mortality models (Akushevich et al., 2005, Manton et al., 2008). There was no significant effect of birth cohort found. Parameter estimates of the dynamic model show that the tendency in change of AMMI is conserved with time (positive estimate of the effect of the "Difference of recent AMMI", Δ_{13}) with deceleration or tendency to leveling-off (negative estimate of "Recent AMMI", C_1). The effect of age is positive thus reflecting increased multimorbidity with aging. Estimates of birth cohort effects were significant and positive. This means that multimorbidity is increased in the population even after controlling by age. These estimates reflect our observations in Figure 3 on increased patterns of multimorbidity in the general population. This observation can be explained by an increase in diagnoses at earlier stages with time (e.g., due to screening strategies and improved diagnostics).

Validation. To perform a model validation study we separated the NLTCS pooled cohort into two subcohorts of equal size: estimation and validation datasets. The validation procedure included two steps. At the first stage we estimated the model using the estimation dataset and then tested how well the fitted model predicts mortality outcomes in the validation dataset. This procedure can be formalized in terms of ROC curves and the areas under the curves. Figure 4 provides the ROC curves and AUC for several models. It shows that the quality of prediction is excellent. The main finding in these studies is that although the quality of mortality prediction is reasonably good for CCI (the area under curve (AUC) is 0.84, i.e., approximately 84% of the cases of next month survival status are predicted correctly), prediction is much better for AMMI (AUC=0.90). Another

conclusion is that the results are stable with respect to using alternative assumptions for model construction. At the second stage we simulated individual trajectories using the fitted model using measured initial stage in the validation cohort. As expected the prediction of mortality outcomes in the first year is excellent (85-90%) but is not so good for longer time periods such as 5-years (68-75%). This indicates that incidence and recovery models could be improved.

Discussion and Conclusion

A new multimorbidity index (AMMI) reflecting recent innovations in prevention and treatment was developed for the US older adult population and estimated using information from Medicare data. The stages of AMMI development included i) identification of multimorbidity patterns (or disease clusters) most often occurring for older adults, ii) estimates of weights of specific diseases/disease clusters, and iii) evaluating disease indicators during individual follow-up. A population model for predicting all-cause mortality among US older adults in the 2000s based on comorbidity/multimorbidity indices was developed and estimated.

Two Medicare-linked datasets (SEER-Medicare and NLTCS-Medicare) were used in analyses. Estimates of empirical patterns and model parameters obtained using both datasets were in good agreements.

We detected an increase in the AMMI over time which originates not only from individual aging but also due to a cohort effect. An increase in diagnoses at earlier stages is one explanation of the cohort effect.

Predictive models for mortality and AMMI dynamics were developed and then estimated and validated using Medicare data. The models demonstrate excellent capabilities for predicting mortality rates. These models can be used for construction of short-term prediction of mortality and health of US elderly population and for the analysis of “what-if” scenarios by consideration of specific interventions e.g., the strategies of secondary prevention, new therapeutic approaches, and projected Medicare policy changes.

In summary, this new index (AMMI) provides advances in both public health and medical expenditures projecting, and allows for deeper insights into mechanisms underlying morbidity and survival trends.

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Table 1. ICD-9-CM codes for disease clusters contributing to AMMI.

System	*Disease (ICD-9-CM)*
Circulatory	*Hypertension (401-405), MI (410), Other IHD (411, 413, 414), Endo/Pericardium (420-424), Cardiomyopathy (425, 429, 422), ARR (426, 427), HF (428), Stroke (430-437, 348), Stroke with complications (438, 342, 344), Atherosclerosis (440, 272), Peripheral Vein (451-454, 456, 459), Aneurysm/Arterial Embolism/Thrombosis (441-445, 447, 557).*
Neoplasms	*NonSolid (200-208), Fem. Breast (174), Pancreas (157), Kidney (189), Prostate (185), Melanoma (172), Lung (162), Colorectal (153, 154), Other Solid Fast Progressive, Other Solid Slow Progressive, MTS (196-198), Other Nonspecified (199, 238, 239).*
Respiratory	*COPD (490-496), Pulmonary Heart (415, 416, 514), Pneumonia (480-488), Other Lung (510-519).*
Mental	*Dementia/Alzheimer (290,294,331.0,331.1,331.2,331.9), Parkinson (332, 331.82), Depression (301.12, 300.4,309.0,309.1,296.2,296.3,296.5,298.0,311) Alcohol abuse (305.0, 357.5, 425.5, 535.3, 571.0-571.3, 291, 303, 980), Drug/Medicine Abuse (292, 304.1, 305.4, 305.8, 305.9), Tobacco abuse(989.84, V15.82, 305.1).*
Endocrine	*Diabetes (250), Electrolytes (276).*
Digestive/	*Chronic Liver (571-573, 0702-0707, 0709), IBD (556, 555, 558, 538), Ulcer (531-534),*
Renal	*Gastrointestinal hemorrhage/bleeding (578),Renal (580-589, V56, 593).*
Infectious	*Septicemia (038), HIV (042).*
Blood	*Anemia (286.5, 286.7, 286.9, 280, 281, 283-285, 287, 289, V78).*
Injury	*Up./Lo. Limb Fracture (V82.81, V54.13, V13.5, 905.2-905.5, 810-813, 817-821, 823-825, 827, 828, 733, V54).*
Other	*RA (714,725), Senility (797), Low Weight (783.2, 783.7, 799.4, 783.0, 783.3, 783.9, 260-263).*

Table 2. Disease Specific Weights: Estimates using SEER-Medicare

Disease	RR_{uni}	RR_{mul}	Disease	RR_{uni}	RR_{mul}
Heart failure	3.23	1.79	COPD	2.24	1.33
Myocardial infarction	2.85	1.13	Pulmonary Heart	3.56	1.12
Other IHD	1.75	1.00	Pneumonia	3.08	1.29
Endo/Pericardium	1.90	0.98	Other Lung Disease	3.33	1.24
Cardiomyopathy	2.28	1.07	Dementia/Alzheimer's Dis.	3.11	1.80
Cardiac arrhythmia	2.01	1.09	Parkinson's Disease	2.73	1.59
Hypertension	1.25	0.82	Depression	1.84	1.03
Cerebrovascular disease (CRVSD)	2.33	1.25	Alcohol abuse	3.67	1.82
CRVSD with complications	3.11	1.44	Tobacco abuse	2.57	1.24
Atherosclerosis	1.03	0.76	Drug/Medicine abuse	2.68	1.07
Diseases of peripheral veins	1.91	0.98	Diabetes	1.93	1.41
Aneurysm/Embolism/Thrombosis	2.05	1.21	Electrolytes	3.14	1.23
Leukemias and lymphomas	3.48	1.92	Chronic Liver Disease	2.70	1.20
Fem. Breast Cancer	1.55	1.13	IBD	1.40	0.82
Pancreas Cancer	6.98	3.24	Ulcer	1.70	0.86
Kidney Cancer	2.61	1.20	Gastrointestinal bleeding	2.31	1.04
Prostate Cancer	1.77	1.26	Renal Disease	3.52	1.55
Melanoma	1.44	0.94	Septicemia	5.18	1.27
Lung Cancer	9.18	3.06	HIV/AIDS	8.15	4.48
Colorectal Cancer	2.60	1.43	Anemia	2.27	1.21
Solid cancers (fast progression)	3.32	1.60	Up./Lo. Limb Fracture	1.47	1.00
Solid cancers (slow progression)	1.23	1.03	Rheumatoid arthritis	1.30	0.98
MTS	8.33	2.90	Senility	2.11	1.11
Other nonspecified Cancer	1.93	1.05	Weight deficiency	3.05	1.34

Table 3. Parameter estimates for mortality and dynamic models given by equations (1) and (2)

	NLTCS-Medicare		SEER-Medicare	
Parameter	Estimate	p-value	Estimate	p-value
Mortality Model				
Intercept	-7.31	<.0001	-7.40	<.0001
Recent AMMI	0.437	<.0001	0.429	<.0001
3-month-prior AMMI	-0.154	<.0001	-0.163	<.0001
Age	0.067	<.0001	0.079	<.0001
Birth Cohort	-0.004	0.37	0.007	0.14
Dynamic Model				
Intercept	0.067	<.0001	0.061	<.0001
Recent AMMI	-0.042	<.0001	-0.038	<.0001
Difference of recent AMMI	0.079	<.0001	0.076	<.0001
Age	0.0068	<.0001	0.0069	<.0001
Birth Cohort	0.002	<.0001	0.003	<.0001

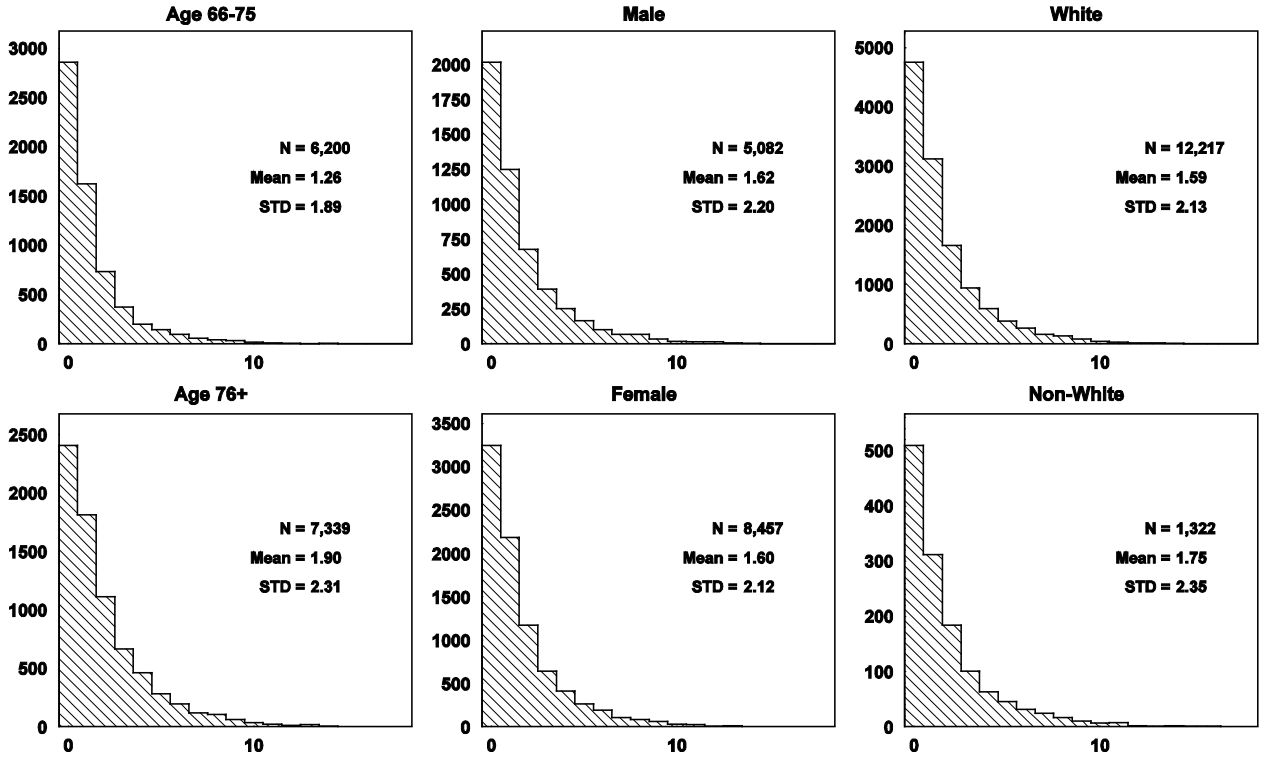

Figure 1. Empirical distributions of AMMI for various population groups calculated for the NLTCS-Medicare data.

Figure 2. Time-dependence of AMMI for the two cohorts of NLTCS-Medicare data (upper plots) and for SEER-Medicare population (Lower plots).

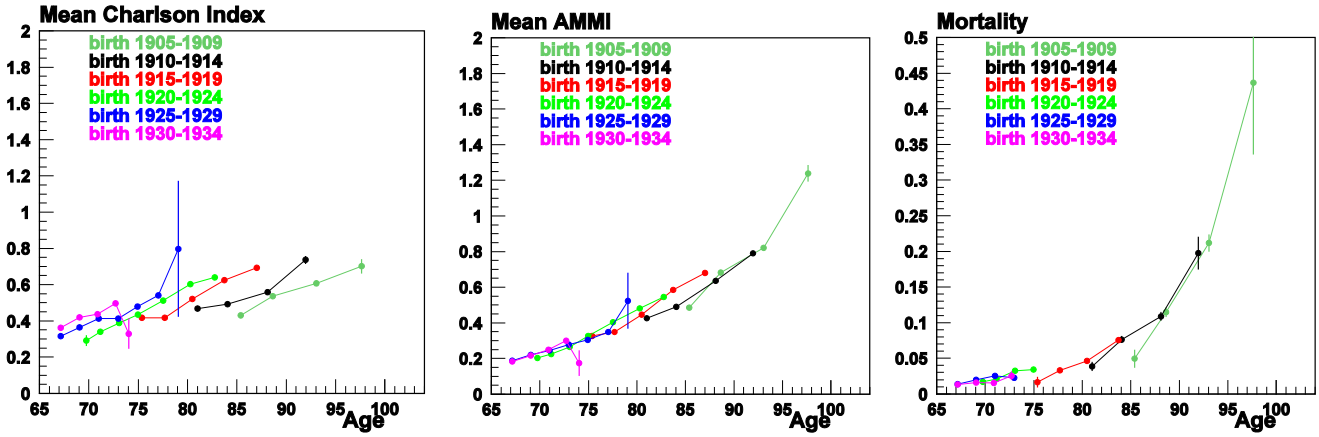

Figure 3. Sex specific age-patterns of the AMMI and mortality rate for female cohorts with standard errors

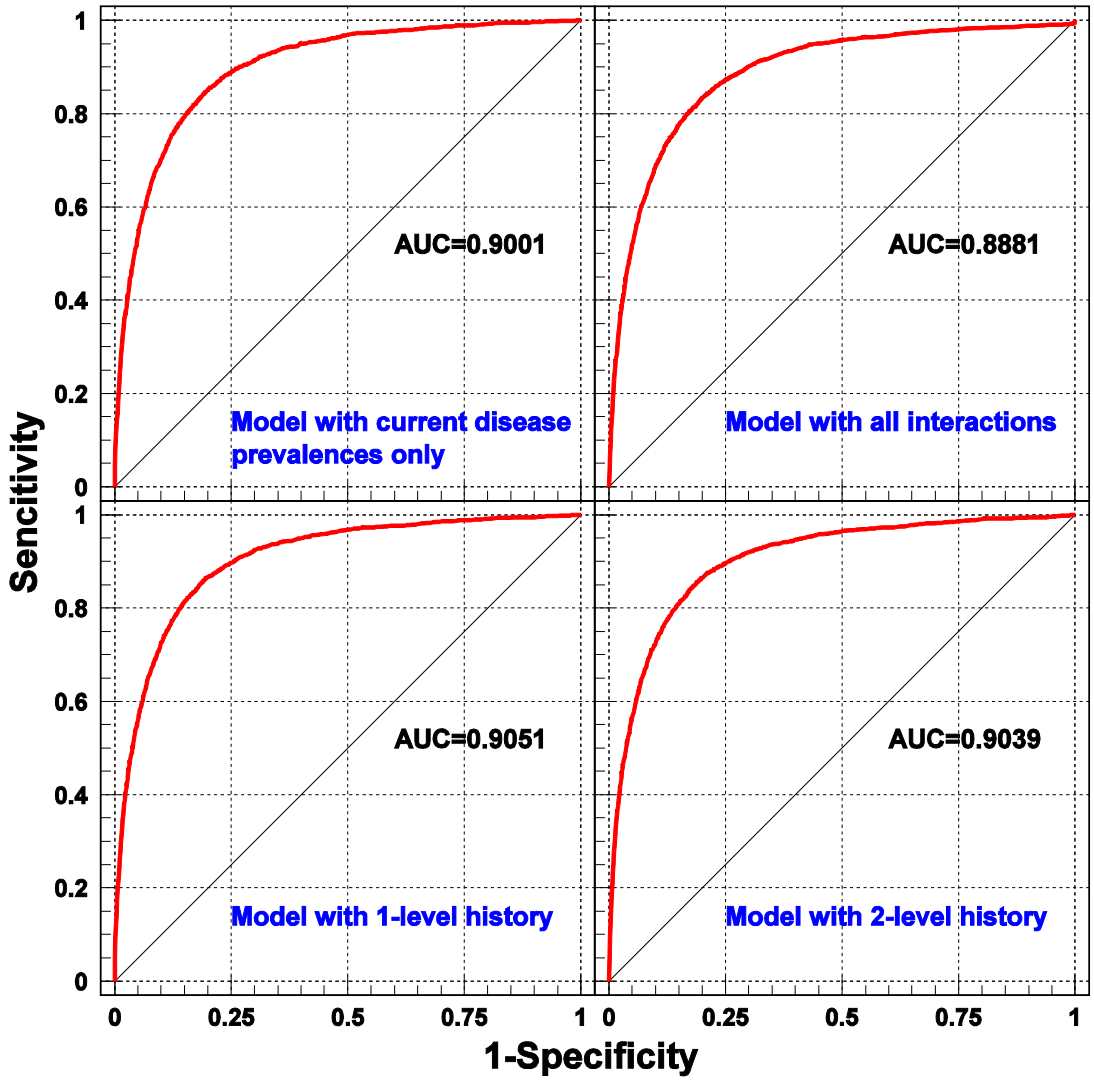

Figure 4. ROC curves and AUC values for several selected models.