Chapter - 2

Review of Literature

The reviewed literatures were presented in order of the following broad categories:

2.1: Survival Analysis

An observational study conducted by Chakravarty et al [39] to assess the factors determining survival of patients on ART under routine programme conditions in an ART centre in north India. A total of 1689 patients were included in the analysis, of whom 272 (16.1%) expired, 205 (12.1%) were lost to follow up (LFU), 526 (31.1%) were transferred out to other facilities and 686 (40.6%) were alive at the end of two years. Majority (92%) of the deaths occurred in the first six months of therapy. Age > 30 yr, male gender, poor functional status, haemoglobin level < 11 g/dl, body weight < 45 kg and CD4 count < 100/µl at baseline had significantly higher relative hazard of death. Most LFU also occurred in the first six months and these patients had significantly low CD4 count, weight, haemoglobin level and higher number of patients in Stages III and IV as compared to those who survived. The study findings revealed the poor survival in first six months of therapy especially in those with severe immunosuppression. This emphasizes the need for early enrolment into the programme. The high LFU occurring early after initiation of therapy suggests the urgent need to build an efficient patient retrieval system in the programme.

Damtew et al [40] conducted a retrospective cohort study to assess the survival and identified predictors of death in adult HIV-infected patients initiating ART at a public hospital in Eastern Ethiopia. Time to death was the main outcome measure. Kaplan-Meier plots were used to estimate mortality and Cox proportional hazards models to identify predictors of mortality. A total of 784 patients (58.4% females) were followed for a median of 60 months. There were 87 (11.1%) deaths yielding an overall mortality rate of 5.15/100 PYO (95% CI: 4.7-6.4). The estimated mortality was 8.4%, 9.8%,
11.3%, 12.7% and 14.1% at 6, 12, 24, 36 and 48 months respectively. The independent predictors of death were single marital status (AHR: 2.31, 95% CI: 1.2-4.5), a bedridden functional status (AHR: 5.9, 95% CI: 2.9-12.2), advanced WHO stage (AHR: 7.4, 95% CI: 3.2-17.1), Body Mass Index (BMI) < 18.5 Kg/m² (AHR: 2.2, 95% CI: 1.2-4.1), CD4 count < 50 cells/μL (AHR: 2.7, 95% CI: 1.3-5.8), severe anemia (AHR: 4.6; 95% CI: 2.3-9.1), and Tuberculosis (TB) co-infection (AHR: 2.3, 95% CI: 1.3-4.1). Improved survival was observed in patients taking ART in Somali region of Ethiopia. Intensive case management was recommended for patients with the prognostic factors.

Mallitt et al [41] assessed the ART use in Armenia and its impact on the number of AIDS diagnoses and mortality using national surveillance data. Cox-proportional hazard model was used to determine the effect of demographic and clinical risk factors, including access to ART, on AIDS and mortality. Among people diagnosed with HIV since 2005, approximately 40% per year were diagnosed with CD4 < 200 cells/mL. Overall, 232 people (57.1%) with AIDS or a low CD4 count had not received ART by the end of 2010. Mortality was 34.1% among people living with HIV who did not initiate ART, and 0.3% among people who received ART. Among people diagnosed with HIV from 1996 to 2010, age at diagnosis, no use of ART, likely mode of transmission, likely place of transmission, low baseline CD4 count and no STI diagnosis at last contact are significantly associated with death. Of people diagnosed with HIV and in need of ART, a large proportion (approximately 60%) either did not provide consent for treatment or were migrants who cannot be located. Globally, the scale-up of ART has resulted in substantial reductions in mortality among individuals initiating therapy.

A retrospective cohort study by Tancredi and Waldman [42] aimed to compare mortality rates and survival in a cohort of AIDS patients before and after the introduction of antiretroviral drugs (ARV) and investigated the predictors of survival in the city of Sao Paulo. All patients were recruited from an STD/HIV outpatient clinic between 1988 and 2003 and followed up until 2005. The Cox proportional hazards model was used to assess predictors of survival in AIDS patients. The study cohort comprised 6,594 patients. The
yearly mean mortality rates were 17.6, 23.2, and 7.8 per 1,000 person-years for the study periods 1988–1993, 1994–1996, and 1997–2003, respectively. Median survival time was 13.4 and 22.3 months for patients entering the study in the first and second study periods and survival time was 108 months or more in 72% of those entering the study during 1997–2003. Factors independently associated with shorter survival included: AIDS diagnosis during the 1994–1996 (AHR: 2.0) and 1988–1993 (AHR: 3.2) periods; 50 years of age or more (AHR: 2.0); exposure category of injection drug users (IDU) (AHR: 1.5); 8 years of schooling or less (AHR: 1.4); no schooling (AHR: 2.1); and CD4 counts between 350 and 500 cells/mm$^3$ (HR: 1.2) and less than 350 cells/mm$^3$ at AIDS diagnosis (HR: 1.3). The study showed a strong impact following the introduction of HAART in 1996 with decreased AIDS mortality, increased survival rates, and benefits with early introduction of HAART. However, some groups of patients were less likely to benefit from the new drug regimens.

Adamu et al [43] described the survival status and identified the determinant factors associated with mortality in a cohort of HIV infected patients treated with HAART. The study included 832 patients who treated with HAART in Jimma University Specialized Hospital from 2003-2007. Kaplan-Meier survival curves and Log-Rank test were used to compare the survival experience of different groups of patients and proportional hazards Cox model was used to explore the factors associated with increased risk of mortality. Some 144 patients died during the follow up time of which 48.6% and 68.8% deaths occurred within three and six months of HAART initiation, respectively. The overall mean estimated survival time of patients was 63.7 months. Factors associated with increased risk of mortality were older age (HR: 1.0, 95% CI: 1.1-1.5), low CD4 count at baseline (HR: 0.9, 95% CI: 0.9-0.1.0), low weight at baseline (HR for a 5kg change: 0.9, 95% CI: 0.8-1.0), bedridden and ambulatory functional status (HR: 6.9, 95% CI: 4.0-11.9) and (HR: 2.8, 95% CI: 1.9-4.4), respectively, co-infection with TB (HR: 1.9, 95% CI: 1.3-2.8) and substance use (HR: 1.4, 95% CI: 1.0-1.9). The study recommended early
diagnosis and treatment should be encouraged and focus should be given in these predictors.

Bhatta et al [44] assessed the mortality rates and determinants among adult HIV-infected patients on ART in Far-western region of Nepal. This retrospective cohort study included 1024 (51.2% men) HIV-infected patients aged ≥15 years who started ART between May 15th 2006 and May 15th 2011 in five ART sites in the Far-western region of Nepal. Follow-up time was calculated from the date of ART initiation to date of death or censoring. Mortality rates (per 100 person-years) were calculated. Kaplan-Meier and Cox-regression models were used to estimate survival and explore determinants of mortality. The median follow-up time was 19.1 months. The crude mortality rate was 6.3 (95% CI: 5.3-7.6) but more than three-times higher in first 3 months after ART initiation (21.9 (95% CI: 16.6- 28.8)). About 12% (83% men) of those newly initiated on ART died during follow-up. The independent determinants of mortality were male sex (AHR: 4.55; 95% CI 2.4-8.5), poor baseline performance scale (bedridden <50% of the day during the past month, AHR: 2.1, 95% CI: 1.2-3.5; bedridden >50% of the day during the past month, AHR: 3.4, 95% CI: 1.7-6.9 compared to normal activity), one standard deviation decrease in baseline bodyweight (AHR: 1.0, 95% CI 1.0-1.1), and poor WHO clinical stage (stage III, AHR: 2.9, 95% CI: 1.3-6.7; stage IV, AHR: 3.3, 95% CI: 1.3-8.3 compared to WHO clinical stage I or II). This study reported that high mortality was observed within the first 3 months of ART initiation. Patients with poor baseline clinical characteristics had higher mortality, especially men.

Hambisa et al [45] have tried to identify the determinants of mortality among HIV positives after initiating ART. A retrospective cohort study was conducted among 416 ART attendees enrolled between July 2005 to January 2012 in Nekemte Referral Hospital, Western Ethiopia. Actuarial table was used to estimate survival of patients after ART initiation and log rank test was used to compare the survival curves. Cox proportional hazard regression was applied to determine the independent determinants of time to death. The estimated mortality was 4%, 5%, 6%, 7%, and 7% at 6, 12, 24, 36 and
48 months respectively with mortality incidence density of 1.89 deaths per 100 person years (95% CI: 1.7-3.6). Forty years and above (AHR: 3.1, 95% CI: 1.3-7.2), low baseline hemoglobin level (AHR: 0.5, 95% CI: 0.3-0.8), and poor ART adherence (AHR: 27.9, 95% CI: 8.9-86.8) were found to be an independent determinants of mortality.

Labhardt et al [46] compared outcomes between patients who started ART at HCs and hospitals in two rural catchment areas in Lesotho. The two catchment areas comprise two hospitals and 12 HCs. Patients ≥ 16 years starting ART at a hospital or HC between 2008 and 2011 were included. Loss to follow-up (LFU) was defined as not returning to the facility for ≥ 180 days after the last visit, no follow-up as not returning after starting ART, and retention in care as alive and on ART at the facility. The data were analyzed using logistic regression, competing risk regression and Kaplan-Meier methods. Multivariable analyses were adjusted for sex, age, CD4 cell count, World Health Organization stage, catchment area and type of ART. All analyses were stratified by gender. Of 3747 patients, 2042 (54.5%) started ART at HCs. Both women and men at hospitals had more advanced clinical and immunological stages of disease than those at HCs. Over 5445 patient-years, 420 died and 475 were LTFU. Kaplan-Meier estimates for three-year retention were 68.7 and 69.7% at HCs and hospitals, respectively, among women (p = 0.81) and 68.8% at HCs versus 54.7% at hospitals among men (p < 0.001). These findings persisted in adjusted analyses, with similar retention at HCs and hospitals among women (OR: 0.9, 95% CI: 0.7-1.1) and higher retention at HCs among men (OR: 1.5, 95% CI: 1.2-1.9). The latter result was mainly driven by a lower proportion of patients LTFU at HCs (OR: 0.7, 95% CI: 0.5-0.93). This study concluded the overall retention in care did not differ significantly between nurse-led HCs and hospitals.

Poka-Mayap et al [47] assessed the incidence and determinants of mortality among patients with HIV-1 infection who were started on ART in a referral treatment centre for HIV infection in Yaounde, Cameroon. Cohort study was designed with baseline assessment between 2007 and 2008, and follow-up during 5 years until June 2012 in Yaounde Jamot Hospital, Cameroon. All-cause mortality over time; accelerated failure
time models used to relate baseline characteristics to mortality occurrence during follow-up. Of the 1444 patients included, 827 (53.7%) were men, and the median age (25–75th centiles) was 38 (31–45) years. The median duration of follow-up was 14.1 (1.1–46.4) months, during which 235 deaths were recorded (cumulative incidence rate: 16.3%), including 208 (88.5%) during the first year of follow-up. Baseline predictors of mortality were male gender (AHR: 2.2, 95% CI: 1.3-3.5), active tuberculosis (AHR: 2.35, 95% CI: 1.4-3.9), WHO stages III–IV of the disease (AHR: 3.6, 95% CI: 1.3-10.2), low weight (AHR: 1.0, 95% CI: 1.0-1.1)/kg, low CD4 count (AHR: 1.0, 95% CI: 1.0-1.1)/10/mm³ lower CD4) and low haemoglobin levels (AHR: 1.12, 95% CI: 1.0-1.3)/g/dL lower). Mortality rate among the patients with HIV was very high within the first year of starting ART in this centre. Early start of the treatment at a less advanced stage of the disease, and favorable levels of CD4 could be reduced early mortality.

Mossong et al [48] used sex- and age-specific HIV prevalence data from an ongoing population-based demographic and HIV survey to infer HIV incidence and survival in rural KwaZulu-Natal between 2003 and 2011, a period when antiretroviral treatment (ART) was rolled out on a large scale. Catalytic mathematical model was used for estimating HIV incidence and differential survival in HIV-infected persons on multiple rounds of HIV sero-prevalence. The study evaluated trends of HIV incidence and survival by estimating parameters separately for women and men aged 15-49 years during three calendar periods (2003-05, 2006-08, 2009-2011) reflecting increasing ART coverage. Median survival after HIV infection increased significantly between 2003-2005 and 2009-2011 from 10.0 (95% CI: 8.8-11.2) to 14.2 (95% CI: 12.6-15.8) years in women (p < 0.001) and from 10.0 (95% CI: 9.2-10.8) to 14.0 (95% CI: 10.6-17.4) years in men (p = 0.02). The model suggested no statistically significant reduction of HIV incidence in the age-group 15-49 in 2009-2011 compared to 2003-2005. Age- and sex-specific model-based HIV incidence estimates were in good agreement with observed cohort-based estimates from the ongoing HIV surveillance.
Rai et al [49] examined the effect of optimal adherence to ART on survival status of HIV infected patients attending ART centers in Jharkhand, India. Data from a cohort of 239 HIV infected individuals who were initiated ART in 2007 were compiled from medical records retrospectively for 36 months. Socio-demographic characteristics, CD4 count, presence of opportunistic infections at the time of ART initiation and ART regimen intake and survival status was collected periodically. Optimal adherence was assessed using pill count methods; patients who took, 95% of the specified regimens were identified as non-adherent. Cox-proportional hazard model was used to determine the relative hazards of mortality. More than three-fourths of the patients were male, on an average 34 year old and median CD4 T cell count was 118 cells/cmm at the time of ART registration. About 57% of the patients registered for ART were found to be adherent to ART. A total of 104 patients died in 358.5 patient-years of observation resulting in a mortality rate of 29 per 100 patient-years (95% CI: 23.9–35.2) and median survival time of 6.5 months (CI: 2.7–10.9). The mortality rate was higher among patients who were non-adherent to ART (64.5, CI: 50.5–82.4) than who were adherent (15.4, CI: 11.3–21.0). The risk of mortality was fourfold higher among individuals who were non-adherent to ART than who were adherent (AHR: 3.9, CI: 2.6–6.0). Adherence to ART is associated with a higher chance of survival of HIV infected patients, ascertaining the need for interventions to improve the ART adherence and early initiation of ART.

Ryavanki et al [50] made an attempt to describe the general profile of adult HIV patients and provided an estimate of survival probabilities following the time of diagnosis and initiation of antiretroviral therapy and its relation with WHO staging and CD4 count. The study was based on secondary data of HIV-positive patients registered at ART centre, New Civil Hospital, Surat, Gujarat, India from September 2006 to December 2010 and followed-up till January 2011. Individuals with age >15 years and had required information for analysis were included. Death of HIV patient was considered as outcome. Descriptive statistics to describe general profile, Kaplan-Meier Method for survival probability and Log rank test for significance was used. Cox's proportional hazards used
to look for association between variables and survival. The proportions of males were 66%. Age group 25-45 years contributes 77% of cases. Majority of patients were married (75%). Survival probability after 15 years of diagnosis of HIV was 83%. The 4 year survival probability was 88% after the start of ART. The crude mortality rate was 8.6%. The mortality density was 10.8 per 1000 person years. The marital status and gender were not associated with survival. WHO clinical staging 3 and 4, CD4 count < 200, and age > 55 years have poor survival. There was significant difference in survival among different WHO clinical stages but no significant difference in survival between CD4 count 200-250, 250-350, 350-500 and > 500. The study concludes that the new WHO guideline to start ART when CD4 count is < 350 can cause financial burden to provide free ART without survival advantage.

Biadgilign et al [51] conducted a five years retrospective cohort study among HIV infected patients on ART to examine the mortality and its predictors in eastern Ethiopia. Cox regression and Kaplan-Meier analyses were performed to investigate factors that influence time to death and survival over time. A total of 1540 study participants were included in the study. From the registered patients in the cohort, the outcome of patients as active, deceased, lost to follow up and transfer out was 1005 (67.2%), 86 (5.9%), 210 (14.0%) and 192 (12.8%) respectively. The overall mortality rate provides an incidence density of 2.03 deaths per 100 person years (95% CI: 1.6-2.5). Out of a total of 86 deaths over 60 month period; 63 (73.3%) died during the first 12 months, 10 (11.6%) during the second year, and 10 (11.6%) in the third year of follow up. In multivariate analysis, the independent predictors for mortality were loss of more 10% weight loss, bedridden functional status at baseline, ≤ 200 CD4 cell count/ml, and advanced WHO stage patients. A lower level of mortality was detected among the cohort of patients on antiretroviral treatment in eastern Ethiopia.

Assefa and Wencheko [52] estimated the mortality rate and identified the predictors that have significant impact on the survival status of a sample of patients who received antiretroviral treatment and care in Tikur Anbessa Specialized Hospital, Addis Ababa,
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Ethiopia during 2005-08. Out of a population of HIV-patients who were taking antiretroviral therapy in the hospital in that period, data on 1,000 patients were used for this study with age range 15 to 75 years. The Kaplan-Meier Method was employed to estimate mortality; the Cox Proportional Hazards Regression Method was used to identify determinants of mortality. After initiation of the antiretroviral treatment, HIV-positive patients lived for an average of 5.6 years (CI: 3.6-7.6 years); the median survival age was found to be 3.98 years (CI: 2.9-4.9 years). The number of medications, baseline functional status, CD4 count, antiretroviral treatment, age, gender and weight impact the survival experience of the patients. Antiretroviral therapy treatment reduced death among AIDS patients by 50 percent.

Apidechkul [53] conducted a retrospective cohort study with a systematic data extraction of medical records of hill tribe HIV/AIDS cases receiving medical care in 37 hospitals situated in 4 provinces of northern Thailand. Survival analysis and Cox’s-Regression were employed in statistical interpretation. A total of 608 case records were scrutinized, of which 581 were suitable for analyses. 81.0% of subjects were alive at the time of our study, 64.9% were female, 39.6% were 26-35 years of age at time of diagnosis. 36.2% were Lahu, 29.8% were Karen, 57.7% were Buddhist, and 24.6% were Christian. 57.5% were infected by sexual transmission, 6.2% were intra venous drug users (IDU). Those receiving antiretroviral drugs (ARV) had a median survival time of 12.4 years, whereas the non-ARV group had a median survival time of 5.9 years (p < 0.01). Median survival time of those with non-opportunistic infections was 10.6 years, whereas it was 6.3 years for the opportunistic infection (OI) group (p < 0.01). Median survival time of females was 6.6 years and 12.4 years for males (p < 0.01). Five-year survival rate was 74.1% (95%CI: 67.9-79.1), and 10-year survival rate was 64.4% (95% CI: 54.8-72.5). Cox’s-regression model found that being female (HR: 0.5, 95% CI: 0.2-0.8), receiving ARV (HR: 0.4, 95% CI: 0.2-0.7), and having non-OI (HR: 0.5, 95% CI: 0.1-0.9) were factors favoring good survival.

Lifson et al [54] conducted a study to identify factors associated with increased risk of
post-HAART mortality among U.S. military personals. They evaluated baseline (prior to HAART initiation) clinical, demographic and laboratory factors (including CD4 count and HIV RNA level) for associations with subsequent mortality in 1,600 patients who began HAART in a prospective observational cohort of HIV-infected U.S. military personnel. Cumulative mortality was 5%, 10% and 18% at 4, 8 and 12 years post-HAART. Mortality was highest (6.23 deaths/100 person-years) in those with ≤ 50 CD4 cells/mm$^3$ before HAART initiation, and became progressively lower as CD4 counts increased (0.70/100 PY with ≥ 500 CD4+ cells/mm$^3$). In multivariate analysis, factors significantly (p < 0.05) associated with post-HAART mortality included: increasing age among those ≥ 40 years (HR: 1.3 per 5 year increase), clinical AIDS events before HAART (HR: 1.9), ≤ 50 CD4+ cells/mm$^3$ (vs. CD4 ≥ 500, HR: 2.9), greater HIV RNA level (HR: 1.3 per one log10 increase), hepatitis C antibody or chronic hepatitis B (HR: 1.9), and HIV diagnosis before 1996 (HR: 2.4). Baseline CD4 = 51-200 cells (HR: 1.7, p = 0.06), and hemoglobin < 12 gm/dL for women or < 13.5 for men (HR: 1.3, p = 0.07) were borderline significant. Although treatment had improved HIV survival, defining those at greatest risk for death after HAART initiation, including demographic, clinical and laboratory correlates of poorer prognoses.

Mageda et al [55] examined mortality rates and its predictors from a five years retrospective cohort data of HIV/AIDs patients attending care and treatment clinic in Biharamulo Tanzania. Cox regression analysis was used to identify predictors of mortality. Of the 546 patient records retrieved, the mean age was 37 years with median CD4 count of 156 cells. The mortality rate was 4.32/100 person years at risk with males having three times higher mortality compared to females. Starting Antiretroviral treatment with advanced disease state, body weight below 45 kegs, WHO stage 4 disease, and CD4 cells below 50 were main predictors of mortality.

McManus et al [56] examined long-term survival in HIV-positive patients receiving cART in the Australian HIV Observational Database (AHOD), to describe changes in mortality compared to the general population and developed longer-term survival models.
Data were examined from 2,675 HIV-positive participants in AHOD who started cART. Standardised mortality ratios (SMR) were calculated by age, sex and calendar year across prognostic characteristics using Australian Bureau of Statistics national data as reference. SMRs were examined by years of duration of cART by CD4 and similarly by viral load. Survival was analyzed using Cox-proportional hazards and parametric survival models. The overall SMR for all-cause mortality was 3.5 (95% CI: 3.0–4.0). SMRs by CD4 count were 8.6 (95% CI: 7.2–10.2) for CD4 < 350 cells/ml; 2.1 (95% CI: 1.5–2.9) for CD4 = 350–499 cells/ml; and 1.5 (95% CI: 1.1–2.0) for CD4 ≥ 500 cells/ml. SMRs for patients with CD4 counts, 350 cells/mL were much higher than for patients with higher CD4 counts across all durations of cART. SMRs for patients with viral loads greater than 400 copies/ml were much higher across all durations of cART. Multivariate models demonstrated improved survival associated with increased recent CD4, reduced recent viral load, younger patients, absence of HBVsAg-positive ever, year of HIV diagnosis and incidence of ADI. Parametric models showed a fairly constant mortality risk by year of cART up to 15 years of treatment. Observed mortality remained fairly constant by duration of cART and was modeled accurately by accepted prognostic factors. These rates did not vary much by duration of treatment. Changes in mortality with age were similar to those in the Australian general population.

Gadpayle et al [57] estimated survival function of AIDS patient who were diagnosed at an ART centre and whether age, gender, stages, and mode of transmission affect survival of AIDS patients on HAART. The study included 344 AIDS patients who were followed-up at an anti-retroviral therapy centre (ART) of a teaching hospital. The records of the patients undergoing treatment were retrospectively analyzed for various demographic variables, survival and mortality rate over a period of 6 years. The study included a cohesive treatment of censored observations based on lost to follow-up or deaths till the end of study as well as uncensored observations. The trend of survivability with respect to age, sex, stages, and mode of transmission was studied across these 6 years. Kaplan-Meier method was used to estimate survival function with respect to gender and mode of
transmission. Cox proportional hazard model was applied for the prediction of significant prognostic factors related to survival time. Age at the time of diagnosis was inversely correlated to survival in AIDS patients: median survival time was 5.66 ± 1.38, 5.1 ± 1.76 and 4.59 ± 1.73 years for children (0-14 years), youth (15-35 years), and adults (> 35 years) respectively. Sex of the patient had no significant effect on the survival of the patients. AIDS patients who were intravenous drug users and were in stage IV of disease had the worst survival rates amongst all groups. Even in the HAART era, age of the patient and mode of transmission are important prognostic factors in predicting the survival of AIDS patients.

Cavanaugh et al [58] analyzed culture-confirmed, pulmonary TB among patients with TB and HIV in the United States from 1993–2008 to calculate prevalence ratios (PRs) for smear-negative disease by demographic and clinical characteristics. Allowing two years for treatment outcome to be reported and hazard ratios (HRs) determined for survival by smear status, adjusted for significant covariates on patients before 2006. Among 16,710 cases with sputum smear results, 6,739 (39%) were sputum smear-negative and 9,971 (58%) were sputum smear-positive. The prevalence of smear-negative disease was lower in male patients (PR: 0.8, 95% CI: 0.8–0.9) and in those who were homeless (PR: 0.9, CI: 0.8–0.9) or used alcohol excessively (PR: 0.91, CI: 0.8–0.9), and higher in persons diagnosed while incarcerated (PR: 1.2, CI: 1.1–1.3). Patients with smear-negative disease had better survival compared to patients with smear-positive disease, both before (HR: 0.8, CI: 0.7–0.9) and after (HR: 0.8, CI: 0.7–0.9) the introduction of combination anti-retroviral therapy. In the United States, smear-negative pulmonary TB in patients with HIV was not associated with higher mortality, in contrast to what had been documented in high TB burden settings. This difference could contribute to diagnostic and treatment delays in high-burden countries, possibly resulting in higher mortality.

Cornell et al [59] examined the magnitude of and risk factors for gender differences in mortality on ART. They analyses included 46,201 ART-naive adults starting ART between January 2002 and December 2009 in eight ART programmes across South
Africa (SA). Patients were followed from initiation of ART to outcome or analysis closure. The primary outcome was mortality; secondary outcomes were loss to follow-up (LTF), virologic suppression, and CD4 cell count responses. Survival analyses were used to examine the hazard of death on ART by gender. Sensitivity analyses were limited to patients who were virologically suppressed and patients whose CD4 cell count reached 200 cells/ml. We compared gender differences in mortality among HIV+ patients on ART with mortality in an age-standardised HIV-negative population. Among 46,201 adults (65% female, median age 35 years), during 77,578 person-years of follow-up, men had lower median CD4 cell counts than women (85 versus 110 cells/ml, p = 0.001), were more likely to be classified WHO stage III/IV (86 versus 77%, p<0.001), and had higher mortality in crude (8.5 versus 5.7 deaths/100 person-years, P<0.001) and adjusted analyses (AHR: 1.3, 95% CI: 1.2–1.4). After 36 months on ART, men were more likely than women to be truly LTF (AHR: 1.2, 95% CI: 1.1–1.3) but not to die after LTF (AHR: 1.0, 95% CI 0.8–1.3). Findings were consistent across all eight programmes. Virologic suppression was similar by gender; women had slightly better immunologic responses than men. Notably, the observed gender differences in mortality on ART were smaller than gender differences in age-standardised death rates in the HIV-negative South African population. Over time, non-HIV mortality appeared to account for an increasing proportion of observed mortality.

Bakanda et al [60] developed an observational study of patients who started cART at The AIDS Service Organization (TASO) in Uganda between 2004 and 2009. Age was stratified into three groups: children (≤ 10 years), adolescents (11–19 years), and adults (≥ 20 years). Kaplan-Meier survival curves were generated to describe time to mortality and loss to follow-up, and Cox regression used to model associations between age and mortality and loss to follow-up. To address loss to follow up, we applied a weighted analysis that assumes 50% of lost patients had died. A total of 23,367 patients were included in this analysis, including 810 (3.5%) children, 575 (2.5%) adolescents, and 21,982 (94.0%) adults. A lower percentage of children (5.4%) died during their cART
treatment compared to adolescents (8.5%) and adults (10%). After adjusting for confounding, other features predicted mortality than age alone. Mortality was higher among males (p<0.001), patients with a low initial CD4 cell count (p<0.001), patients with advanced WHO clinical disease stage (p < 0.001), and shorter duration of time receiving cART (p<0.001). The crude mortality rate was lower for children (22.8 per 1000 person-years; 95% CI: 16.1-29.5), than adolescents (36.5 per 1000 person-years; 95% CI: 26.3-46.8) and adults (37.5 per 1000 person-years; 95% CI: 35.9-39.1). This study was the largest assessment of adolescents receiving cART in Africa.

Mills et al [61] aimed to determine if men have differing outcomes from women across a nationally representative sample of adult patients receiving combination antiretroviral therapy in Uganda. The study estimated survival distributions for adult male and female patients using Kaplan-Meier, constructed multivariable regressions to model associations of baseline variables with mortality and also assessed person-years of life lost up to age 55 by sex. To minimize the impact of patient attrition, it was assumed a weighted 30% mortality rate among those lost to follow up. Study included data from 22,315 adults receiving antiretroviral therapy. At baseline, men tended to be older, had lower CD4 baseline values, more advanced disease, had pulmonary tuberculosis and had received less treatment follow up ( p < 0.001). Loss to follow up differed between men and women (7.5 versus 5.9%, p < 0.001). Over the period of study, men had a significantly increased risk of death compared with female patients (AHR: 1.4, 95% CI 1.3-1.5, p < 0.001). The crude mortality rate for males differed importantly from females (43.9, 95% CI: 40.7-47.0/1000 person-years versus 26.9, 95% CI: 25.4-28.5/1000 person years, p < 0.001). The probability of survival was 91.2% among males and 94.1% among females at 12 months. Person-years of life lost were lower for females than males (689.7 versus 995.9 per 1000 person-years, respectively).

Alemu and Sebastian [62] aimed to assess the early survival outcome of the scale-up service by utilizing routine hospital data. All adult HIV/AIDS patients who started on antiretroviral treatment in Shashemene and Assela hospitals from January 1, 2006 to May
31, 2006 were included and followed up for 2 years. Data were extracted from standard patient medical registrations. Kaplan-Meier curves were used to estimate survival probability and the Cox proportional hazard model was applied to determine predictors of mortality. Two alternative assumptions (real case and worst case) were made in determining predictors of mortality. The median age of patients was 33 years and 57% were female. Eighty-five percent had CD4 ≤ 200 cells/mL with a median CD4 count of 103 cells/mL. The median survival time was 104.4 weeks. A total of 28 (10.3%) deaths were observed during the 2-year period and 48 patients (18%) were lost to follow up. The majority of deaths occurred in the first 4 months of treatment. In multivariate analysis, 2-year survival was significantly associated with the clinical stage of the disease, baseline hemoglobin, and cotrimoxazole prophylaxis therapy (CPT) at or before ART initiation in both assumptions. The median CD4 count and body weight showed a marked improvement during the first 6 months of treatment, followed by stagnation thereafter. The study showed an overall low mortality but a high loss to follow-up rate of the cohort. Advanced clinical stage, anemia, low body weight, and lack of CPT initiation were independent predictors of mortality - but not gender. CPT initiation should be encouraged in routine HIV care services, and patient retention mechanisms have to be strengthened. Study recommended that stagnation in immunological and weight recovery after the first 6 months should be further investigated and utilization of routine data should be encouraged in order to facilitate appropriate decision making.

Bachani et al [63] aimed to analyze treatment outcomes of patients receiving first-line antiretroviral therapy (ART) through the national AIDS control programme of India. Using routinely collected programme data specifically analyzed mortality, CD4 evolution and adherence outcomes over a 2-year period in 972 patients who received first-line ART between 1 October 2004 and 31 January 2005 at 3 government ART centers. Cox regression analysis was used to identify independent predictors of mortality. Of the 972 patients (median age: 35-years, 66% men), 71% received the stavudine/ lamivudine/ nevirapine regimen. The median CD4 count of enrolled patients was119 cells/cmm (IQR
50–200 cells/cmm) at treatment initiation; 44% had baseline CD4 count < 100 cells/cmm. Of the 927 patients for whom treatment outcomes were available, 71% were alive after 2 years of treatment. The median increase in CD4 count was 142 cells/cmm (IQR 57–750 cells/cmm; n=616) at 6 months and 184 cells/cmm (IQR 102–299 cells/cmm; n=582) at 12 months after treatment. Over 2 years, 124 patients (13%) died; the majority of deaths (68%) occurred within the first 6 months of treatment. Those with baseline CD4 count < 50 cells/cmm were significantly more likely to die (AHR: 2.5, 95% CI: 1.3–3.2) compared with patients who had baseline CD4 count > 50 cells/cmm. Over the 2-year period, 323 patients (35%) missed picking up their monthly drugs at least once and 147 patients (16%) were lost to follow up. Survival rates of HIV-infected patients on first-line ART in India were comparable with those from other resource-limited countries and concluded that most deaths occurred early and among patients who had advanced disease.

Harrison et al [64] estimated life expectancy and average years of life lost (AYLL) after an HIV diagnosis using population-based surveillance data from 25 states that had name-based HIV surveillance since 1996. They used US national HIV surveillance data (cases ≥ 13 years old) to model life expectancy after an HIV diagnosis using the life table approach. They compared life expectancy at HIV diagnosis with that in the general population of the same age, sex, and race/ethnicity in the same calendar year using vital statistics data to estimate the AYLL due to an HIV diagnosis. Average life expectancy after HIV diagnosis increased from 10.5 to 22.5 years from 1996 to 2005. Life expectancy (years) was better for females than for males but improved less for females (females: 12.6–23.6 and males: 9.9–22.0). In 2005, life expectancy for black males was shortest, followed by Hispanic males and then white males. AYLL for cases diagnosed in 2005 was 21.1 years (males: 19.1 and females: 22.7) compared with 32.9 years in 1996. Disparity in life expectancy for females and both black and Hispanic males, compared with males and white males, respectively, persists and should be addressed.

Johansson et al [65] estimated mean life years gained using different treatment indications in low income countries. They carried out a systematic search to identify
relevant studies on the treatment effect of HAART. Outcome from identified observational studies were combined in a pooled-analyses and applied these data in a Markov life cycle model based on a hypothetical Tanzanian HIV population. Survival for three different HIV populations with and without any treatment is estimated. The number of patients included in the pooled-analysis was 35,047. Providing HAART early for CD4 count 200-350 cells/μl was likely to be the best outcome strategy with an expected net benefit of 14.5 life years per patient. The model predicts diminishing treatment benefits for patients starting treatment when CD4 counts were lower. Patients starting treatment at CD4; 50-199 and <50 cells/μl have expected net health benefits of 7.6 and 7.3 life years. Without treatment, HIV patients with CD4 counts 200-350; 50-199 and < 50 cells/μl can expect to live 4.8; 2.0 and 0.7 life years respectively. This study demonstrates that HIV patients live longer with early start strategies in low income countries. Since low income countries have many constraints to full coverage of HAART, this study provided input to a more transparent debate regarding where to draw explicit eligibility criteria during further scale up of HAART.

Kee et al [66] investigated survival times, survival characteristics, and changes in survival after initial HIV diagnosis. Survival was characterized by evaluation of the immune status at primary HIV diagnosis nationwide. A total of 5,323 HIV-infected individuals were registered with the government and followed until the end of 2007. Survival following HIV diagnosis was estimated based on epidemiological characteristics. They examined 3,369 individuals with available initial CD4 cell counts within 6 months of HIV diagnosis to estimate survival based on immune status at diagnosis. The association between epidemiological variables and survival times was analyzed with univariate and multivariate Cox's proportional hazards model. Individuals died during the study period (n = 980), and 45% of the individuals died within 6 months of HIV diagnosis. The median survival following HIV diagnosis was 16.7 years. Survival were longer in women, in younger persons, in individuals diagnosed at blood centers, and in individuals diagnosed later in the study period. Survival were shortest in individuals
with CD4 cell counts < 200 cells/mm$^3$ at HIV diagnosis. These results suggest that early HIV diagnosis in Korea may be imperative to increase survival and to promote the quality of life for HIV-infected individuals with governmental support. The median survival time of HIV-infected individuals following HIV diagnosis was 16.7 years in Korea. The survival was significantly lower in individuals with CD4 cell counts < 200 cells/mm$^3$ at HIV diagnosis and higher by introduction of drugs and development of therapy.

Dias et al [67] investigated the predictors of mortality in HIV associated hospitalizations in Portugal through a hierarchical survival model. The study population consists of 12,078 adult discharges from patients with HIV infection diagnosis attended at Portuguese hospitals from 2005–2007 that were registered on the diagnosis-related groups' database. They used discharge and hospital level variables to develop a hierarchical model. The discharge level variables were: age, gender, type of admission, type of diagnoses-related group, related HIV complication, the region of the patient's residence, the number of diagnoses and procedures, the Euclidean distance from hospital to the centroid of the patient's ward, and if patient lived in the hospital's catchment area. The hospital characteristics include size and hospital classification according to the National Health System. Kaplan-Meier plots were used to examine differences in survival curves. Cox proportional hazard models with frailty were applied to identify independent predictors of hospital mortality and to calculate hazard ratios (HR). The Cox proportional model with frailty showed that male gender, older patient, great number of diagnoses and pneumonia increased the hazard of HIV related hospital mortality. On the other hand tuberculosis was associated with a reduced risk of death. Central hospital discharge also presents less risk of mortality. The frailty variance was small but statistically significant, indicating hazard ratio heterogeneity among hospitals that varied between 0.67 and 1.34, and resulted in two hospitals with HR different from the average risk. The frailty model suggested that the unmeasured factors affecting mortality in HIV associated
hospitalizations. Consequently, for healthcare policy purposes, hospitals should not all be treated in an equal manner.

Velasco et al [68] assessed the effect of HAART on the survival of patients with TB. They selected all HIV patients included in the COMESEM cohort with TB diagnosis after 1996. Clinical and epidemiological data were registered. They compared patients who started HAART at the diagnosis of TB [simultaneous therapy (ST)] or not. Survival was assessed by Cox analysis. Among the 6934 HIV patients included in the cohort, 1217 patients had TB, 322 of them (26.5%) after 1996. At the time of TB diagnosis, 45% of them started HAART (ST). There were no differences between groups regarding basal characteristics, except for a lower viral load in ST patients. ST therapy was associated with improved survival (HR: 0.4, 95% CI: 0.2-0.7, P = 0.003). By univariate analysis, survival was also associated with no endovenous drug use and a later year of TB diagnosis. After adjusting for other prognostic variables, by Cox multivariate analysis, ST remained robustly associated with improved survival (AHR: 0.4, 95% CI: 0.2-0.7, P = 0.001). Simultaneous HAART and TB treatment in HIV patients with TB is associated with improved survival.

Harrison et al [69] estimated relative survival (RS) after human immunodeficiency virus (HIV) diagnosis, by race/ethnicity and county-level socioeconomic status (SES). Authors have estimated 5-year RS by age, race/ethnicity, transmission category, sex, diagnosis year, CD4 count, and by county-level SES variables from the U.S. Census. Data, from the national HIV/AIDS Reporting System, were for HIV-infected persons ages >13 years (diagnosis during 1996–2003 and follow-up through 2005). They calculated RS proportions by using a maximum likelihood algorithm and modeled the relative risk of excess death (RR) using generalized linear models, with poverty as a random effect. For men, RS was worse in counties with larger proportions of people living below the 2000 U.S. poverty level (87.7% for poverty of >20% vs. 90.1% for poverty of <5.0%) and where unemployment was greater (87.8% where unemployment > 7.1% vs. 90.5% where unemployment < 4.0%). The effects of county-level SES on RS of women were similar.
In multilevel multivariate models, RR for men and women within 5 years after an HIV diagnosis was significantly worse in counties where 10.0–19.9% (compared with <5.0%) lived below the poverty level (RR Z: 1.3, 95% CI: 1.2–1.5; and RR Z: 1.8, 95% CI: 1.4–2.2, respectively). RS was worse in lower SES areas. To help address the impact of county-level SES, resources for HIV testing, care, and proven economic interventions should be directed to areas with concentrations of economically disadvantaged people.

Fang et al [70] provided the life expectancy of patients with newly-diagnosed HIV infection in the era of highly active antiretroviral therapy (HAART) using a semi-parametric projection. Follow-up data for patients newly diagnosed with HIV infection in Taiwan (HIV/AIDS Cohort) from 1 May 1997 to 30 April 2003 (n = 3351, only 1% are injecting drug users) were analyzed using the Kaplan-Meier method. The survival function for an age- and gender-matched reference population was generated by the Monte Carlo method from the life-table of the general population. A constant excess hazard model was used to project long-term survival of HIV-infected patients, with linear extrapolation of a logit-transformed curve of survival ratio between HIV-infected patients and the reference population. The 5-year survival rate was 58% in patients who had already developed AIDS at diagnosis (AIDS group), and 89% in those who had not (non-AIDS group). Extrapolation yielded an expected mean survival time of 10.6 years after diagnosis for the AIDS group, and 21.5 years after diagnosis for the non-AIDS group. Our results support the expansion of HIV screening programs to minimize delay in diagnosis. With continuing advances in HAART, this estimate of survival in initially asymptomatic patients may be conservative. Their long life expectancy raises questions about what kind of preventive health services should be offered. These should be addressed through further analysis of overall benefit and cost-effectiveness.

Lima et al [71] characterized the temporal changes in mortality and life expectancy among HIV-positive individuals initiating antiretroviral therapy in British Columbia, Canada, from 1993 to 2004. This analysis was restricted to 2238 antiretroviral-naive HIV-positive individuals who started antiretroviral therapy between January 1993 and
September 2004. The primary analysis endpoint was all-cause mortality stratified by four time periods: 1993–1995, 1996–1998, 1999–2001, and 2002–2004. Cox proportional hazard models, with associated 95% confidence intervals (CI), were used to estimate the hazard of death. Abridged life tables were constructed to compare life expectancies at the age of 20 years. Product limit estimates of the cumulative mortality rate at 12 months after therapy initiation decreased from 15.8% (±1.6%) in 1993–1995 to 6.1% (±1.1%) in 2002–2004. Life expectancy at the age of 20 years has increased from 9.1 years (±2.3 years) in 1993–1995 to 23.6 years (±4.4 years) in 2002–2004. Subjects in 1993–1995 were more likely to die than those who started therapy in 2002–2004 (HR: 2.8; 95% CI: 1.9–3.8). Patients who initiated dual therapy or therapies containing three or more antiretroviral drugs were, respectively, 1.49 (95% CI: 1.2–1.8) and 2.56 (95% CI: 2.1–3.1) times less likely to die than those who started on monotherapy. A significant and progressive decrease in mortality and increase in life expectancy were observed over the 12-year study period. The increase in life expectancy and decrease in mortality were directly associated with the use of modern forms of HAART.

Zhang [72] used generalized linear models with Poisson error to investigate HIV/AIDS relative survival. Relative excess risk of death within 3 years after HIV/AIDS diagnosis was significantly higher for non-Hispanic blacks, American Indians and Hispanics compared with non-Hispanic Whites. Excess hazard of death was also higher among male injection drug users compared with men who have sex with men (MSM). The relative excess hazard of old HIV/AIDS patients was significantly higher compared with younger patients (e.g., 60+ age group vs 19-29 year age group). When CD4 increased, the relative excess hazard decreased; while with the increase of HIV viral load, the relative excess hazard decreased. These population-based results showed that viral load was a determinant risk factor of disease progression after HIV infection; basically the mean residual life has similar trend to relative survival.

Campos et al [73] studied and compared survival rates using the Brazilian Ministry of Health 2004 and Centers for Disease Control and Prevention (CDC) 1993 case definitions
in a large HIV/AIDS referral centre in Rio de Janeiro. Survival after AIDS diagnosis was assessed in a clinic-based cohort of 1415 individuals using the Kaplan–Meier method and Cox proportional hazards models. There were 393 (88%) deaths from AIDS-related causes and 52 (12%) from unrelated or unknown causes. A total of 205 patients (14%) were lost to follow-up and 765 patients (55%) remained alive until the end of the study. Three-quarters of patients (75%) were still alive 22 months (95% CI: 19–26) after the AIDS diagnosis according to the CDC case definition and 31 months (95% CI: 26–36) according to the Ministry of Health case definition. Independent predictors of survival included AIDS defined by CD4 cell count and any use of highly active antiretroviral therapy, with either case definition and initial stage of the case with the Ministry of Health case definition. Survival observed in this reference centre was comparable or longer than other international studies, although the choice of case definition criterion influenced findings. Adoption of the Ministry of Health case definition may enhance the ability to track the use of and outcomes from ART among AIDS patients [73].

Chow et al [74] studied and identified measurable factors at the time of diagnosis that predict the progression to Acquired Immunodeficiency Syndrome (AIDS) among Human Immunodeficiency Virus (HIV)-infected patients in Singapore. They carried out a retrospective study of 790 HIV-infected patients from 16 May 1985 to 31 December 2001. The end-point was the onset of AIDS-defining illness listed in the 1987 and 1991 revised Centers for Disease Control and Prevention criteria, but excluded CD4 cell counts as a criterion. Using the Kaplan-Meier method, AIDS-free survival curves were plotted for age groups at diagnosis, baseline CD4 counts and periods for utilization of antiretroviral treatment. A Cox regression model was constructed to determine independent predictors of disease progression. Univariate analysis showed that patients of older age at diagnosis had a significantly higher risk of progression compared to younger patients, and patients with higher baseline CD4 cell counts had a lower risk of progression to AIDS. Adjusting for the simultaneous influence of several covariates on the rate of HIV progression to AIDS, multivariate analysis using the Cox model showed a
significantly higher risk of progression for older patients at diagnosis, and the progressive lowering of risk with increasing baseline CD4 cell counts. This study found older age at diagnosis and baseline CD4 cell counts to be measurable predictors for HIV progression to AIDS at time of diagnosis. Identification of these risk factors might enables physicians to provide counselling and advice, and to start appropriate treatment early. This could lower the risk of progression and improve survival.

King et al [75] constructed a computer simulation model based on observational data to estimate long-term survival in a cohort of HIV/AIDS patients undergoing treatment with HAART. The authors used data from the Collaboration in HIV Outcomes Research-US (CHORUS) observational cohort (N = 4791), the published literature, and US Life Tables to specify a computer simulation model of expected survival accounting for baseline CD4 cell count, progressive HAART treatment failure, progressive risk of HAART on treatment mortality, and age-associated mortality. Time to treatment failure for each of three rounds of HAART and risk of mortality on-treatment were estimated using parametric survival models with censoring of follow-up fit to CHORUS data. Off-treatment survival after HAART failure was estimated from the pre-HAART literature. Age-associated mortality was taken from US Life Tables. Median projected survivals stratified by baseline CD4 cell count subgroups were CD4 > 200 cells/mm$^3$, 15.4 years; CD4 ≤ 200 cells/mm$^3$, 8.5 years; and CD4 ≤ 50 cells/mm$^3$, 5.5 years. These values were 4 to 6 years longer than pre-HAART cohorts. The sensitivity analyses showed that the model survival predictions were most sensitive to the treatment failure rate, the on-treatment mortality rate, and the number of treatment rounds. Computer simulation modeling of long-term survival of patients with HIV/AIDS on HAART accounting for differential treatment failure and death rates stratified by CD4 cell count and age-associated mortality suggests a relatively consistent 4- to 6-year survival benefit over pre-HAART therapies.

Marins et al [76] conducted a national level study among Brazilian AIDS patients to examine the impact of universal free access to antiretroviral treatment since 1996. Using
national data for cases diagnosed in 1995 and 1996 with randomly selected 3930 adult AIDS cases from 18 cities in seven states representing all regions of Brazil. Trained abstracters reviewed medical records, determining dates of diagnosis and death or last contact, exposure category, treatment, and demographics. After review, 2821 cases met the inclusion criteria and were available for Kaplan–Meier and proportional hazards analysis. Data from the earlier study were re-analyzed for comparison. Median survival was 5 months for cases diagnosed in the 1980s, 18 months for those diagnosed in 1995, and 58 months for those diagnosed in 1996. Predictors of longer survival in univariate analysis included antiretroviral treatment, year of diagnosis, higher education, sexual exposure category, female sex, and Pneumocystis carinii pneumonia prophylaxis. In multivariate analysis, the predictive value of most of these was attenuated or disappeared, leaving antiretroviral treatment as the main predictor of survival. Survival time has increased substantially for adult Brazilian AIDS patients. The timing of these gains and analysis of the predictors of survival both indicate antiretroviral treatment as the cause. These findings demonstrate that universal access to antiretroviral treatment in a developing country can produce benefits on the same scale as in richer countries.

Montgomery et al [77] examined the association between access to care and survival time after progression to AIDS, using survival analysis methods. This study combined data from two CDC sponsored studies of HIV-infected persons, a cross-sectional interview study and a longitudinal medical record review study. Study subjects included 752 persons who progressed to AIDS before December 31, 1999, and were patients at either of two major HIV care facilities in Detroit, MIchigan. Separate statistical models were used to test associations between survival time after meeting the criteria for AIDS and two indicators of access to health care: (1) perceived access to health care and (2) health care utilization patterns. Perceived access was not associated with survival time after AIDS, but patterns of health care utilization were significantly associated with survival time after AIDS (HR: 5 2.0, \( p < 0.001 \)). Individuals who received a greater proportion of
their care in the ER had a worse survival prognosis than those who received more of their health care in an outpatient clinic setting.

Rogers et al [78] studied the survival of HIV/AIDS-patients in the United Kingdom (UK). Data from 13,689 adult AIDS cases diagnosed up to the end of 1996 were analysed. The overall median survival from AIDS diagnosis to death was 19.3 months. Over 50% of the cases diagnosed in 1996 were alive at the end of the survey therefore median survival exceeds 24 months, the maximum follow up time for the cohort. The opportunity for receiving HAART was modeled in three time periods: pre-multiple therapies (before September 1995), multiple reverse-transcriptase inhibitor therapy available (September 1995 to March 1996), and multiple therapy including protease inhibitors available (April 1996 onwards). Survival rates improved significantly among female heterosexuals and men who have sex with men when multiple therapy including protease inhibitors became available.

Li et al [79] described the pattern of survival following AIDS using national surveillance for AIDS data. AIDS cases in adults/adolescents (aged ≥ 13 years at AIDS diagnosis) and deaths following AIDS were notified to the national HIV surveillance centre by the diagnosing doctor through State/Territory health authorities. The date of last medical contact for each case living with AIDS was updated annually. By 30 June 1999, 4814 AIDS cases, diagnosed in Australia in 1991±1996, and 3193 deaths following AIDS had been noticed to the National AIDS Registry. Median survival following AIDS was 17.7 months. Survival following AIDS increased from 16.0 months in 1991 to 27.7 months in 1996. Factors independently associated with improved survival were year of AIDS diagnosis, late HIV diagnosis, CD4 Cell count greater than 50 × 10⁶ cells/l, age of less than 45 years and presentation with Pneumocystis carinii pneumonia only or Kaposi's sarcoma only. The risk of death declined over time when the initial AIDS-defining illness was Pneumocystis carinii pneumonia only [AHR: 0.9, P<0.0005]; other opportunistic infections (AHR: 0.9, P<0.0005); Kaposi's sarcoma only (AHR, 0.9, P<0.025); and central nervous system conditions (HIV encephalopathy, cryptococcosis, toxoplasmosis)
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(AHR: 0.9, P=0.012). No time trend was observed for survival following diagnoses of non-Hodgkin's lymphoma or other multiple illnesses. Survival following AIDS was improved in Australia, especially among cases diagnosed in 1995 and 1996. Temporal improvements in survival following AIDS were coincident with the introduction of combination antiretroviral treatment for HIV infection and suggest that treatment is effective in limiting disease progression among people with advanced HIV infection.

Amo et al [80] examined differences in progression to AIDS and death between HIV-positive Africans (most infected in sub-Saharan Africa and therefore with non-B subtypes) and HIV-1-positive non-Africans in London. Retrospective cohort study of 2048 HIV-1-positive individuals attending 11 of the largest HIV/AIDS units in London was designed. Subjects were 1056 Africans and 992 non-Africans seen between 1982–1995. There were no differences in crude survival from presentation to death between Africans and non-Africans (median 82 and 78 months, respectively; \( P = 0.22 \)). Africans progressed more rapidly to AIDS (HR: 1.2, 95% CI: 1.0–1.5) but after adjustment for age, sex, Centers for Disease Control and Prevention category B symptoms and CD4+ lymphocyte count at presentation, year of HIV diagnosis and hospital attended, this difference was no longer significant (AHR: 1.2, 95% CI: 0.9–1.4). Africans with AIDS had a reduced risk of death compared with non-Africans (HR: 0.8; 95% CI: 0.6–0.9) but not after adjustment for age, CD4 lymphocyte count at AIDS, initial AIDS defining conditions (ADC) and hospital attended (HR: 0.9, 95% CI: 0.7–1.3). Tuberculosis as the first ADC was associated with a 64% reduction in the risk of death. CD4 lymphocyte decline was not significantly different between Africans and non-Africans \( (P = 0.18) \). Differences in progression to AIDS and death and CD4+ lymphocyte decline between HIV-1-infected Africans and non-Africans in London could not be attributed to ethnicity or different viral subtypes. Age and the clinical and immunological stage at presentation, or AIDS, were the major determinants of outcome. Compared with other diagnoses, tuberculosis as the initial ADC was associated with increased survival. Lack of access to health care and exposure to environmental pathogens are the most likely causes of
reduced survival with AIDS in Africa, rather than inherently different rates of progression of immune deficiency due to racial differences or viral subtypes.

2.2 Model validation

Van de Laar [81] validated and compared the performance of three prognostic models for overall survival in patients with advanced-stage epithelial ovarian cancer. A multi-institutional epithelial ovarian cancer database was used to identify patients and to evaluate the predictive performance of two nomograms, a prognostic index and FIGO (International Federation of Obstetrics and Gynecology) stage. All patients were treated for advanced-stage epithelial ovarian cancer between January 1996 and January 2009 in 11 hospitals in the eastern part of The Netherlands. In total, 542 patients were found to be eligible. Overall performance did not differ between the three prognostic models and FIGO stage. The discriminative performance for Chi’s model was moderately good (c indices 0.65 and 0.68) and for the models of Gerestein and Teramukai reasonable (c indices between 0.60 and 0.62). The c indices of FIGO stage ranged between 0.54 and 0.62. After recalibration, the three models showed almost perfect calibration, whereas calibration of FIGO stage was reasonable. The three prediction models showed general applicability and a reasonably well-predictive performance, especially in comparison to FIGO stage. To date, there are no studies available that analyze the impact of these prognostic models on decision-making and patient outcome. Therefore, the usefulness of these models in daily clinical practice remains to be investigated.

Dickman et al [82] discussed the methodology of relative survival and its STATA commands. Now, it became the method of choice for estimating patient survival using data collected by population-based cancer registries. The relative survival ratio is typically estimated from life tables as the ratio of the observed survival of the patients (where all deaths are considered events) to the expected survival of a comparable group from the general population. This article describes the command strs for life table estimation of relative survival. Three methods of estimating expected survival are
available and estimates can be made using a cohort, period, or hybrid approach. A life table version of the Pohar Perme estimator of net survival is also available. Two methods for age standardization are available. Probabilities of death due to cancer and due to other causes can be estimated using the method of Cronin and Feuer. Excess mortality can be modelled using a range of approaches including full likelihood (using the ml command) and Poisson regression (using the glm command with a user-specified link function).

Royston and Altman [83] described statistical approaches to external validation of a published Cox model according to the level of published information, specifically (1) the prognostic index only, (2) the prognostic index together with Kaplan-Meier curves for risk groups, and (3) the first two plus the baseline survival curve (the estimated survival function at the mean prognostic index across the sample). The most challenging task, requiring level 3 information, is assessing calibration, for which we suggest a method of approximating the baseline survival function. Authors applied the methods to two comparable datasets in primary breast cancer, treating one as derivation and the other as validation sample. Results are presented for discrimination and calibration. We demonstrate plots of survival probabilities that can assist model evaluation. Our validation methods are applicable to a wide range of prognostic studies and provide researchers with a toolkit for external validation of a published Cox model.

Mittal et al [84] in their paper, presented tools for fitting regularized Cox survival analysis models on high-dimensional, massive sample-size (HDMSS) data using a variant of the cyclic coordinate descent optimization technique tailored for the sparsity that HDMSS data often present. Experiments on two real data examples demonstrate that efficient analyses of HDMSS data using these tools result in improved predictive performance and calibration.

Chen et al [85] compared the survival-time prediction and survival-time threshold approaches to analyzing cancer survival studies. They reviewed and compared common performance metrics for the two approaches. They presented new randomization tests and
cross-validation methods to enable unambiguous statistical inferences for several performance metrics used with the survival-time prediction approach. We consider five survival prediction models consisting of one clinical model, two gene expression models, and two models from combinations of clinical and gene expression models. A public breast cancer dataset was used to compare several performance metrics using five prediction models. 1: For some prediction models, the hazard ratio from fitting a Cox proportional hazards model was significant, but the two-group comparison was insignificant, and vice versa. 2: The randomization test and cross-validation were generally consistent with the p-values obtained from the standard performance metrics. 3: Binary classifiers highly depended on how the risk groups were defined; a slight change of the survival threshold for assignment of classes led to very different prediction results. The study concludes that: 1) Different performance metrics for evaluation of a survival prediction model may give different conclusions in its discriminatory ability. 2) Evaluation using a high-risk versus low-risk group comparison depends on the selected risk-score threshold; a plot of p-values from all possible thresholds can show the sensitivity of the threshold selection. 3) A randomization test of the significance of Somers’ rank correlation can be used for further evaluation of performance of a prediction model. 4) The cross-validated power of survival prediction models decreases as the training and test sets become less balanced.

Gory et al [86] tried to determine the genes responsible for certain human traits that can be challenging when the underlying genetic model takes a complicated form such as heterogeneity (in which different genetic models can result in the same trait) or epistasis (in which genes interact with other genes and the environment). Multifactor Dimensionality Reduction (MDR) is a widely used method that effectively detects epistasis; however, it does not perform well in the presence of heterogeneity partly due to its reliance on cross-validation for internal model validation. Cross-validation allows for only one “best” model and is therefore inadequate when more than one model could cause the same trait. They hypothesized that another internal model validation method
known as a three-way split will be better at detecting heterogeneity models. In this study, they tested hypothesis by performing a simulation study to compare the performance of MDR to detect models of heterogeneity with the two different internal model validation techniques. They simulated a range of disease models with both main effects and gene-gene interactions with a range of effect sizes. They assessed the performance of each method using a range of definitions of power. Overall, the power of MDR to detect heterogeneity models was relatively poor, especially under more conservative (strict) definitions of power. While the overall power was low, our results show that the cross-validation approach greatly outperformed the three-way split approach in detecting heterogeneity. This may motivate using cross-validation with MDR in studies where heterogeneity might be present. These results also emphasize the challenge of detecting heterogeneity models and the need for further methods development.

Kang et al [87] aimed to develop a model to predict distant recurrence in locally advanced cervical cancer, which can be used to select high-risk patients in enriched clinical trials. They designed a retrospective analysis of a multi-institutional cohort of patients treated between 2001 and 2009. According to the order of data submission, data from three institutions were allocated to a model development cohort (n = 434), and data from the remaining two institutions were allocated to an external validation cohort (n = 115). Patient information including [^{18}\text{F}]\text{ fluorodeoxyglucose} positron emission tomography (FDG-PET) data and clinical outcome was modeled using competing risk regression analysis to predict 5-year cumulative incidence of distant recurrence. The competing risk analysis revealed that the following four parameters were significantly associated with distant recurrence: pelvic and para-aortic nodal positivity on FDG-PET, nonsquamous cell histology, and pretreatment serum squamous cell carcinoma antigen levels. This four-parameter model showed good discrimination and calibration, with a bootstrap-adjusted concordance index of 0.70. Also, the validation set showed good discrimination with a bootstrap adjusted concordance index of 0.73. A user-friendly Web-based nomogram predicting 5-year probability of distant recurrence was developed.
Authors had developed a robust model to predict the risk of distant recurrence in patients with locally advanced cervical cancer. Further, they discussed how the selective enrichment of the patient population could facilitate clinical trials of systemic chemotherapy in locally advanced cervical cancer.

Perme et al [88] discussed the methods of estimation of relative survival that became the first and the most basic step when reporting cancer survival statistics. Standard estimators are in routine use by all cancer registries. However, it has been recently noted that these estimators do not provide information on cancer mortality that is independent of the national general population mortality. Thus they are not suitable for comparison between countries. Furthermore, the commonly used interpretation of the relative survival curve is vague and misleading. The present article attempts to remedy these basic problems. The population quantities of the traditional estimators are carefully described and their interpretation discussed. They proposed a new estimator of net survival probability that enables the desired comparability between countries. The new estimator requires no modeling and is accompanied with a straightforward variance estimate. The methods are described on real as well as simulated data.

Moons et al [89] reviewed that clinical prediction models are increasingly used to complement clinical reasoning and decision-making in modern medicine, in general, and in the cardiovascular domain, in particular. To these ends, developed models first and foremost need to provide accurate and (internally and externally) validated estimates of probabilities of specific health conditions or outcomes in the targeted individuals. Subsequently, the adoption of such models by professionals must guide their decision-making, and improve patient outcomes and the cost-effectiveness of care. In the first paper of this series of two companion papers, issues relating to prediction model development, their internal validation, and estimating the added value of a new (bio) marker to existing predictors were discussed. In this second paper, an overview is provided of the consecutive steps for the assessment of the model’s predictive performance in new individuals (external validation studies), how to adjust or update
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eexisting models to local circumstances or with new predictors, and how to investigate the
impact of the uptake of prediction models on clinical decision-making and patient
outcomes (impact studies). Each step is illustrated with empirical examples from the
cardiovascular field.

Chambless et al [90] discussed the risk prediction under censoring in the survival data
that normally available for fitting the models. This paper remedies that problem. The
primary parameters considered are net reclassification improvement (NRI) and integrated
discrimination improvement (IDI). They have previously similarly considered a primary
measure of concordance, area under the ROC curve (AUC), also called the c-statistic. We
also include here consideration of population attributable risk (PAR) and ratio of
predicted risk in the top quintile of risk to that in the bottom quintile. We evaluated
estimators of these various parameters both with simulation studies and also as applied to
a prospective study of coronary heart disease (CHD). The simulation studies showed that
in general our estimators had little bias, and less bias and smaller variances than the
traditional estimators. They have applied the methods to assessing improvement in risk
prediction for each traditional CHD risk factor compared to a model without that factor.
These traditional risk factors are considered valuable, yet when adding any of them to a
risk prediction model that has omitted the one factor, the improvement is generally small
for any of the parameters. This experience should prepare us to not expect large values of
the risk prediction improvement evaluation parameters for any new risk factor to be
discovered.

Simon et al [91] reviewed methodology for classifying patients into survival risk groups
and for using cross-validation to evaluate such classifications. Measures of discrimination
for survival risk models include separation of survival curves, time-dependent ROC
curves and Harrell’s concordance index. For high-dimensional data applications,
however, computing these measures as re-substitution statistics on the same data used for
model development results in highly biased estimates. Most developments in
methodology for survival risk modeling with high-dimensional data have utilized
separate test data sets for model evaluation. Cross-validation has sometimes been used for optimization of tuning parameters. In many applications, however, the data available are too limited for effective division into training and test sets and consequently authors have often either reported re-substitution statistics or analyzed their data using binary classification methods in order to utilize familiar cross-validation. In this article we have tried to indicate how to utilize cross-validation for the evaluation of survival risk models; specifically how to compute cross-validated estimates of survival distributions for predicted risk groups and how to compute cross-validated time-dependent ROC curves. The study have also discussed evaluation of the statistical significance of a survival risk model and evaluation of whether high-dimensional genomic data adds predictive accuracy to a model based on standard covariates alone.

Campbell et al [92] aimed to estimate and externally validate a new UK-specific prognostic model for predicting the long-term risk of a first recurrent event (local recurrence, metastatic recurrence, or second primary breast cancer) in women diagnosed with early breast cancer. Using data on the prognostic characteristics and outcomes of 1844 women treated for early breast cancer at the Churchill Hospital in Oxford, parametric regression-based survival analysis was used to estimate a prognostic model for recurrence-free survival. The model, which incorporated established prognostic factors, was externally validated using independent data. Its performance was compared with that of the Nottingham Prognostic Index (NPI) and Adjuvant Online. The number of positive axillary lymph nodes, tumor grade, tumor size and patient age were strong predictors of recurrence. Oestrogen receptor (ER) positivity was shown to afford a moderate protective effect. The model was able to separate patients into distinct prognostic groups, and predicted well at the patient level, mean Brier Accuracy Score = 0.17 (S.E. = 0.004) and overall C = 0.745 (95% CI: 0.717–0.773). Its performance diminished only slightly when applied to a second independent data set. When compared with the NPI, the model was able to better discriminate between women with excellent and good prognoses, and it did not overestimate 10-year recurrence-free survival to the
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extent observed for Adjuvant Online. The model estimated here predicts well at both the individual patient and group levels, and appears transportable to patients treated at other UK hospitals. Its parametric form permits long-term extrapolation giving it an advantage over other prognostic tools currently in use. A simple point scoring system and reference table allows 5-, 10-, and 15-year predictions from the model to be quickly and easily estimated.

Steyerberg et al [93] reviewed the performance of prediction models using a variety of methods and metrics. Traditional measures for binary and survival outcomes include the Brier score to indicate overall model performance, the concordance (or c) statistic for discriminative ability (or area under the receiver operating characteristic [ROC] curve), and goodness-of-fit statistics for calibration. Several new measures have recently been proposed that can be seen as refinements of discrimination measures, including variants of the c statistic for survival, reclassification tables, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Moreover, decision–analytic measures have been proposed, including decision curves to plot the net benefit achieved by making decisions based on model predictions. They aimed to define the role of these relatively novel approaches in the evaluation of the performance of prediction models. For illustration, we present a case study of predicting the presence of residual tumor versus benign tissue in patients with testicular cancer (n = 544 for model development, n = 273 for external validation). They suggest that reporting discrimination and calibration will always be important for a prediction model. Decision-analytic measures should be reported if the predictive model is to be used for clinical decisions. Other measures of performance may be warranted in specific applications, such as reclassification metrics to gain insight into the value of adding a novel predictor to an established model.

Karvanen and Harrell [94] presented a graphical method called the rank-hazard plot that visualizes the relative importance of covariates in a proportional hazards model. The key idea was to rank the covariate values and plot the relative hazard as a function of ranks scaled to interval [0, 1]. The relative hazard is plotted with respect to the reference
hazard, which can be, for example, the hazard related to the median of the covariate. Transformation to scaled ranks allows plotting of covariates measured in different units in the same graph, which helps in the interpretation of the epidemiological relevance of the covariates. Rank-hazard plots show the difference of hazards between the extremes of the covariate values present in the data and can be used as a tool to check if the proportional hazards assumption leads to reasonable estimates for individuals with extreme covariate values. Alternative covariate definitions or different transformations applied to covariates can be also compared using rank-hazard plots. We apply rank-hazard plots to the data from the FINRISK study where population-based cohorts have been followed up for events of cardiovascular diseases and compare the relative importance of the covariates cholesterol, smoking, blood pressure and body mass index. The data from the Study to Understand Prognoses Preferences Outcomes and Risks of Treatment (SUPPORT) are used to visualize nonlinear covariate effects. The proposed graphics work in other regression models with different interpretations of the y-axis.

Nelson et al [95] in this paper described the methods for using empirical patient-level data to extrapolate survival in large clinical trials and cohorts beyond a limited follow-up period in which most patients remain alive in order to estimate the entire survival distribution for a cohort of patients. Authors accomplish this task through a novel combination of models that estimate the hazard rate not only as a function of time but also as a function of patient age. Extrapolation of survival beyond a limited time frame is made possible by capitalizing on the extensive latitude of survival information available across the range of ages represented in the data. Variations in approach are presented, and issues arising in these analyses are discussed. The proposed methodology is developed, applied, and evaluated in both a large clinical trial cohort with 5-year follow-up on over 23,000 patients and a large observational database with long-term follow-up on over 4000 patients.

Ahmed et al [96] reviewed the most widely used model for survival analysis, the Cox proportional hazards model because of its simplicity. The fundamental assumption in this
model is the proportionality of the hazard function. When this condition is not met, other modifications or other models must be used for analysis of survival data. They illustrated in this review several methodological approaches to deal with the violation of the proportionality assumption, using survival in colon cancer as an illustrative example.

Remontet et al [97] proposed an overall strategy based on regression models to estimate the relative survival and model the effects of potential prognostic factors. The baseline hazard was modelled until 10 years follow-up using parametric continuous functions. Six models including cubic regression splines were considered and the Akaike Information Criterion was used to select the final model. This approach yielded smooth and reliable estimates of mortality hazard and allowed us to deal with sparse data taking into account all the available information. Splines were also used to model simultaneously non-linear effects of continuous covariates and time-dependent hazard ratios. This led to a graphical representation of the hazard ratio that can be useful for clinical interpretation. Estimates of these models were obtained by likelihood maximization. Authors showed that these estimates could be also obtained using standard algorithms for Poisson regression.

Royston [98] in this article introduced a new measure of explained variation for use with censored survival data. It was a modified version of a measure previously described by Quigley et al, itself a modification of Nagelker’s earlier proposal for a general index of determination. He has also described Stata programs str2ph, which implements the new measure, and str2d, which implements a measure proposed in 2004 by Royston and Sauerbrei. For demonstration purpose, he has provided examples with real data.

Heagerty [99] discussed the predictive accuracy of a survival model can be summarized using extensions of the proportion of variation explained by the model, or $R^2$, commonly used for continuous response models, or using extensions of sensitivity and specificity, which are commonly used for binary response models. In this article, author proposed new time-dependent accuracy summaries based on time-specific versions of sensitivity and specificity calculated over risk sets. Author connected the accuracy that summarized
to a previously proposed global concordance measure, which is a variant of Kendall’s tau. In addition, we show how standard Cox regression output can be used to obtain estimates of time-dependent sensitivity and specificity, and time-dependent receiver operating characteristic (ROC) curves. Semi-parametric estimation methods appropriate for both proportional and non-proportional hazards data are introduced, evaluated in simulations, and illustrated using two familiar survival data sets.

Matheny et al [100] sought to compare the performance of a number of local and well-known mortality models with respect to discrimination and calibration. Accurate risk prediction is important for a number of reasons including physician decision support, quality of care assessment, and patient education. Current evidence on the value of applying PCI risk models to individual cases drawn from a different population is controversial. Data were collected from January 01, 2002 to September 30, 2004 on 5216 consecutive percutaneous coronary interventions at Brigham and Women’s Hospital (Boston, MA). Logistic regression was used to create a local risk model for in-hospital mortality in these procedures, and a number of statistical methods were used to compare the discrimination and calibration of this new and old local risk models, as well as the Northern New England Cooperative Group, New York State (1992 and 1997), University of Michigan consortium, American College of Cardiology-National Cardiovascular Data Registry, and The Cleveland Clinic Foundation risk prediction models. Areas under the ROC (AUC) curves were used to evaluate discrimination and the Hosmer–Lemeshow (HL) goodness-of-fit test and calibration curves assessed applicability of the models to individual cases. Multivariate risk factors included in the newly constructed local model were: age, prior intervention, diabetes, unstable angina, salvage versus elective procedure, cardiogenic shock, acute myocardial infarction (AMI), and left anterior descending artery intervention. The area under the ROC curve (AUC) was 0.929 (S.E. = 0.017), and the p value for the Hosmer–Lemeshow (HL) goodness-of-fit was 0.473. This indicates good discrimination and calibration. Bootstrap re-sampling indicated AUC stability. Evaluation of the external models showed an AUC range from 0.82 to 0.90
indicating good discrimination across all models, but poor calibration (HL p value < 0.0001). Validation of AUC values across all models suggests that certain risk factors have remained important over the last decade. However, the lack of calibration suggests that small changes in patient populations and data collection methods quickly reduce the accuracy of patient level estimations over time. Possible solutions to this problem involve either recalibration of models using local data or development of new local models.

May et al [101] in this paper discussed the flexible parametric models based on the Weibull, loglogistic and lognormal distributions with spline smoothing of the baseline log cumulative hazard function are used to fit a set of candidate prognostic models across k data sets. The model that generalizes best to new data is chosen using a cross-validation scheme which fits the model on k-1 data sets and tests the predictive accuracy on the omitted data set. The procedure is repeated, omitting each data set in turn. The quality of the predictions is measured using three different methods: two commonly proposed validation methods, Harrell's concordance statistic and the Brier statistic, and a novel method using deviance differences. The results show that the deviance statistic is able to discriminate between quite similar models and can be used to choose a prognostic model that generalizes well to new data. The methods are illustrated by using a model developed to predict progression to a new AIDS event or death in HIV-1 positive patients starting antiretroviral therapy.

Pencina and D’Agostino [102] investigated the properties of the overall C index introduced by Harrell as a natural extension of the ROC curve area to survival analysis. Authors have developed the overall C index as a parameter describing the performance of a given model applied to the population under consideration and discuss the statistic used as its sample estimate. We discover a relationship between the overall C and the modified Kendall’s τ and construct a confidence interval for our measure based on the asymptotic normality of its estimate. Then we investigate via simulations the length and coverage probability of this interval. Finally, we present a real life example evaluating the performance of a Framingham Heart Study model.
Clark *et al* [103] discussed methods for analyzing survival time data, both univariate and multivariate. They have dealt with only a portion of the methods available for analyzing survival time data, and in many cases, useful alternatives to (or extensions of) these methods exist. They have also left unanswered other questions regarding the design and analysis of studies that measure survival time and, in particular, dealing with situations where some standard modeling assumptions do not hold. We conclude this series by tackling these issues. These ideas are described in a question and answer format, and introductory references are provided for the reader to investigate further.

Halabi *et al* [104] developed and validated a model that can be used to predict the overall survival probability among metastatic hormone-refractory prostate cancer patients (HRPC). Data from six Cancer and Leukemia Group B protocols that enrolled 1,101 patients with metastatic hormone-refractory adenocarcinoma of the prostate during the study period from 1991 to 2001 were pooled. The proportional hazards model was used to develop a multivariable model on the basis of pretreatment factors and to construct a prognostic model. The area under the receiver operating characteristic curve (ROC) was calculated as a measure of predictive discrimination. Calibration of the model predictions was assessed by comparing the predicted probability with the actual survival probability. An independent data set was used to validate the fitted model. The final model included the following factors: lactate dehydrogenase, prostate-specific antigen, alkaline phosphatase, Gleason sum, Eastern Cooperative Oncology Group performance status, hemoglobin, and the presence of visceral disease. The area under the ROC curve was 0.68. Patients were classified into one of four risk groups. We observed a good agreement between the observed and predicted survival probabilities for the four risk groups. The observed median survival durations were 7.5 (95% CI: 6.2-10.9), 13.4 (95% CI: 9.7-26.3), 18.9 (95% CI: 16.2-26.3), and 27.2 (95% CI: 21.9-42.8) months for the first, second, third, and fourth risk groups, respectively. The corresponding median predicted survival times were 8.8, 13.4, 17.4, and 22.80 for the four risk groups. This model could
be used to predict individual survival probabilities and to stratify metastatic HRPC patients in randomized phase III trials.

Heinze and Schemper [105] developed two SAS macro programs, are presented that evaluate the relative importance of prognostic factors in the proportional hazards regression model and in the logistic regression model. The importance of a prognostic factor is quantified by the proportion of variation in the outcome attributable to this factor. For proportional hazards regression, the program %RELIMPCR uses the recently proposed measure V to calculate the proportion of explained variation (PEV). For the logistic model, the $R^2$ measure based on squared raw residuals is used by the program %RELIMPLR. Both programs are able to compute marginal and partial PEV, to compare PEVs of factors, of groups of factors, and even to compare PEVs of different models. The programs use a bootstrap resampling scheme to test differences of the PEVs of different factors. Confidence limits for P-values are provided. The programs further allowed to base the computation of PEV on models with shrinked or bias-corrected parameter estimates.

Rosen et al [106] determined the validity of a recently developed United Network for Organ Sharing (UNOS) multivariate model using an independent cohort of patients undergoing re-OLT outside the United States, to determine whether incorporation of other variables that were incomplete in the UNOS registry would provide additional prognostic information, to develop new models combining data sets from both cohorts, and to evaluate the validity of the model for end-stage liver disease (MELD) in patients undergoing re-OLT. Two hundred eighty-one adult patients undergoing re-OLT (between 1986 and 1999) at 6 foreign transplant centers comprised the validation cohort. We found good agreement between actual survival and predicted survival in the validation cohort; 1-year patient survival rates in the low-, intermediate-, and high-risk groups (as assigned by the original UNOS model) were 72%, 68%, and 36%, respectively ($P<0.0001$). In the patients for whom the international normalized ratio (INR) of prothrombin time was available, MELD correlated with outcome following re-OLT; the median MELD scores
for patients surviving at least 90 days compared with those dying within 90 days were 20.75 versus 25.9, respectively ($P=0.004$). Utilizing both patient cohorts ($n = 979$), a new model, based on recipient age, total serum bilirubin, creatinine, and interval to re-OLT, was constructed (whole model $\chi^2=105$, $P<.0001$). Using the c-statistic with 30-day, 90-day, 1-year, and 3-year mortality as the end points, the area under the receiver operating characteristic (ROC) curves for 4 different models were compared. In conclusion, prospective validation and use of these models as adjuncts to clinical decision making in the management of patients being considered for re-OLT are warranted.

Schemper [107] discussed the measures of the predictive accuracy of regression models quantify the extent to which covariates determine an individual outcome. Explained variation measures the relative gains in predictive accuracy when prediction based on covariates replaces unconditional prediction. A unified concept of predictive accuracy and explained variation based on the absolute prediction error is presented for models with continuous, binary, polytomous and survival outcomes. The measures are given both in a model-based formulation and in a formulation directly contrasting observed and expected outcomes. Various aspects of application are demonstrated by examples from three forms of regression models. It is emphasized that the likely degree of absolute or relative predictive accuracy often is low even if there are highly significant and relatively strong covariates.

Steyerberg et al [108] evaluated several variants of split-sample, cross-validation and bootstrapping methods with a logistic regression model that included eight predictors for 30-day mortality after an acute myocardial infarction for internal validation. Random samples with a size between $n=572$ and $n=9165$ were drawn from a large data set (GUSTO-I; $n=40,830$; 2851 deaths) to reflect modeling in data sets with between 5 and 80 events per variable. Independent performance was determined on the remaining subjects. Performance measures included discriminative ability, calibration and overall accuracy. We found that split-sample analyses gave overly pessimistic estimates of performance, with large variability. Cross-validation on 10% of the sample had low bias
and low variability, but was not suitable for all performance measures. Internal validity could best be estimated with bootstrapping, which provided stable estimates with low bias. We conclude that split-sample validation is inefficient, and recommend bootstrapping for estimation of internal validity of a predictive logistic regression model.

Altman and Royston [109] reviewed the prognostic models that are used in medicine for investigating patient outcome in relation to patient and disease characteristics. Since, such models do not always work well in practice, so it is widely recommended that they need to be validated. The idea of validating a prognostic model is generally taken to mean establishing that it works satisfactorily for patients other than those from whose data it was derived. In this paper authors have examined the meaning of validation and reviewed why it was necessary. They consider how to validate a model and suggest that it is desirable to consider two rather different aspects - statistical and clinical validity - and examine some general approaches to validation. They also illustrated the issues using several case studies.

Van Houwelingen [110] assessed the validity and value of prognostic survival models presented in the literature for a particular population for which some data has been collected is discussed. Methods are sketched to perform validation through `calibration’ that is by embedding the literature model in a larger calibration model. This general approach is exemplified for x-year survival probabilities, Cox regression and general non-proportional hazards models. Some comments are made on basic structural changes to the model, described as `revision'. Finally, general methods are discussed to combine models from different sources. The methods are illustrated with a model for non-Hodgkin's lymphoma validated on a Dutch data set.

Diciccio and Efron [111] surveyed bootstrap methods for producing good approximate confidence intervals. The goal is to improve by an order of magnitude upon the accuracy of the standard intervals \( \hat{\theta} \pm z^{(\alpha)} \hat{\sigma} \), in a way that allows routine application even to very complicated problems. Both theory and examples are used to show how this is done. In
this article, the first seven sections provide a heuristic overview of four bootstrap confidence interval procedures: BC$_\alpha$, bootstrap-t, ABC and calibration.

Harrell et al [112] discussed the issues and their assumptions in developing a multivariate prognostic model. Multivariable regression models are powerful tools that are used frequently in studies of clinical outcomes. These models can use a mixture of categorical and continuous variables and can handle partially observed (censored) responses. However, uncritical application of modeling techniques can result in models that poorly fit the dataset at hand, or, even more likely, inaccurately predict outcomes on new subjects. One must know how to measure qualities of a model's fit in order to avoid poorly fitted or over-fitted models. Measurement of predictive accuracy can be difficult for survival time data in the presence of censoring. We discuss an easily interpretable index of predictive discrimination as well as methods for assessing calibration of predicted survival probabilities. Both types of predictive accuracy should be unbiasedly validated using bootstrapping or cross-validation, before using predictions in a new data series. We discuss some of the hazards of poorly fitted and over-fitted regression models and present one modeling strategy that avoids many of the problems discussed. The methods described are applicable to all regression models, but are particularly needed for binary, ordinal, and time-to-event outcomes. Methods illustrated with a survival analysis in prostate cancer using Cox regression.

Vervij and Houwelingen [113] constructed a measure of the predictive value of the Cox proportional hazards model, computed from the leave-one-out regression coefficients. These coefficients can also be used to calculate a shrinkage factor which can be applied to improve the predictions and that can be used in R2-type measures of the proportion of explained variation. Our methods are illustrated by a study of chemotherapy for advanced ovarian cancer.