A predictive model of symptoms for pain in independently living frail elderly in palliative care

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Abstract

Background: Life expectancy has increased, causing an increase in the population of frail elderly. Evidence shows that elderly suffer unnecessarily because of widespread underassessment and undertreatment of their health-related problems. In palliative care patients unrelieved pain is a common problem. Effective pain monitoring in elderly includes extra challenges such as age-normative beliefs, underreporting of pain on the part of the patients, proper assessment and atypical manifestations of pain(such as other distressing symptoms). A variety of distressing symptoms correlate with pain in palliative care patients: anxiety, fatigue, loss of appetite, insomnia and dyspnoea. Insight into these symptoms as predictors for pain may help to gain early identification of pain in independently living frail elderly in palliative care.

Aim: To determine whether the symptoms anxiety, fatigue, loss of appetite, insomnia, and dyspnoea are predictors for pain in independently living frail elderly in palliative care and to develop a prediction model.

Method: Cross-sectional study. Community-care nurses from multiple organisations included eligible patients. Utrecht Symptom Diary assessed symptom burden and Case Report Form assessed relevant covariables(age, sex and living situation).

Results: Eighty-three patients were included. Multivariable logistic regression showed presence of dyspnoea as a predicting symptom(p=0.030) and sex(female) as a predicting covariable(p=0.047). Area Under the Curve(=0.723, p=0.001) indicated the accuracy of the final model as fair, with sensitivity of 68.1% and specificity of 66.7%.

Conclusion: This model helps with earlier identification of presence of pain through signalling of presence of dyspnoea and female-sex.

Recommendations: Early identification of pain can help community-care nurses in early advanced care planning by discussing and providing adequate non-pharmacological and pharmacological pain management for independently living frail elderly. Unnecessary suffering from pain may be prevented through early identification with the use of the prediction model.

Keywords: palliative care, frail elderly, pain, symptom assessment, clinical decision rules

Samenvatting

Achtergrond: De levensverwachting neemt toe en dit resulteert in toename van de kwetsbare ouderen populatie. Aangetoond is dat ouderen onnodig lijden door onderrapportage en onderbehandeling van hun gezondheidsproblemen. Niet-verlichte pijn is een bekend probleem bij palliatieve patiënten. Effectieve pijnmonitoring bij ouderen kent een aantal uitdagingen zoals leeftijd-normatieve opvattingen, onderrapportage, juiste beoordeling en atypische manifestatie van pijn(o.a. verontrustende symptomen). Een aantal verontrustende symptomen zijn geassocieerd met pijn bij palliatieve patiënten: angst, vermoeidheid, verlies van eetlust, slaapproblemen en benauwdheid. Inzicht in symptomen als voorspellers voor pijn kan helpen bij het eerder vaststellen van pijn bij thuiswonende kwetsbare ouderen in de laatste levensfase.
Doel: Bepalen of de symptomen angst, vermoeidheid, verlies van eetlust, slaapproblemen en benauwdheid voorspellers zijn voor pijn bij thuiswonende kwetsbare ouderen in de laatste levensfase en een predictiemodel ontwikkelen.
Methode: Cross-sectioneel onderzoek. Wijkverpleegkundigen van meerdere organisaties includeerden geschikte patiënten. Het Utrecht Symptoom Dagboek beoordeelde het symptoomlijden en het Case Report Form verzamelde relevante covariabelen(leeftijd, geslacht en leefsituatie).
Resultaten: Drieëntachtig patiënten werden geïncludeerd. Multivariabele logistische regressie gaf aanwezigheid van benauwdheid als voorspellend symptoom(p=0.030) en geslacht(vrouw) als voorspellende covariabele(p=0.047). Area Under the Curve(=0.723, p=0.001) wees op redelijke accuraatheid van het laatste model, met een sensitiviteit van 68.1% en specificiteit van 66.7%.
Conclusie: Dit model helpt bij het eerder identificeren van pijn door het signaleren van de aanwezigheid van benauwdheid en geslacht(vrouw).
Aanbevelingen: Vroegtijdig vaststellen van pijn kan wijkverpleegkundigen helpen om eerder te beginnen aan advanced care planning door het bespreekbaar maken van en adequaat bieden van niet-farmacologische en farmacologische pijn management bij thuiswonende kwetsbare ouderen in de laatste levensfase. Het predictiemodel kan mogelijk preventie bieden door het vroegtijdig vaststellen van pijn en daarmee onnodig lijden te voorkomen.

Introduction

Life expectancy has increased, causing an increase in the population of elderly (1). The worldwide aged population (≥ 65 years) rapidly grows to an estimated two billion people by 2050 (2). The most problematic remark of population ageing is frailty. Frailty outlines a state of increased vulnerability in older ages which is commonly related with functional limitations and multiple chronic diseases (3). Frail elderly have a high risk of mortality and their age-related decline should be taken into account with planning and delivery of health, social and palliative care (4). According to the World Health Organization (WHO), evidence has shown that older people suffer unnecessarily because of widespread underassessment and undertreatment of their health-related problems (1). Elderly patients diagnosed with life-limiting illnesses report having unmet healthcare needs in palliative care (5).

According to the WHO palliative care is defined as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual” (6). With the aging of the population, the need for good palliative care will increase (7).

Unrelieved pain is a common problem in palliative care patients (8). Pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (9). Approximately 25 million people worldwide die in pain each year (10), and studies show that one-half of patients experience inadequate pain relief (1). According to community surveys, pain is consistently found as an important symptom for one-third of older people (1). The persistence of pain can be a result of the patients terminal illness, their therapeutic treatment or from concomitant diseases (11). Unrelieved pain adds to suffering whether patients have restorative functional goals or are moving on to comfort care (9).

Pain is often underreported in elderly and is partly due to their beliefs that pain is a normal consequence of ageing (12). No studies are found that these “age normative” beliefs are apparent for other distressing symptoms in the last stages of life. Effective pain monitoring in elderly includes challenges such as the underreporting of pain on the part of the patients, proper assessment of pain and atypical manifestations of pain (such as other distressing symptoms) (13).

Pain is a subjective experience involving biological, psychological, social, and spiritual aspects of a person (9). To the concept of total pain, the central belief is that pain emerges from both physical and nonphysical sources (14). The concept recognises that palliative care patients will also suffer from distressing symptoms other than pain. Therefore it is necessary to assess and manage all potential sources of additional distress (15). Pain rarely occurs in

isolation and co-occurring symptoms appear to have synergistic associations with patients' treatment outcomes, prognosis, functional status and quality of life (16).

Cohen and Mount notes a bidirectional relationship: not only does pain affect all aspects of the person, but all aspects of the person can contribute to the perception of pain (17). Other symptoms can contribute to this perception of pain. The five most prevalent symptoms, apart from pain, in elderly palliative cancer-patients are anxiety, fatigue, loss of appetite, insomnia and dyspnoea (range 65 - 92.5%)(18). In the population of palliative care patients or advanced cancer patients, pain has been found to correlate with the aforementioned symptoms; anxiety ($r=0.31$, $p\leq0.05$)(19), loss of appetite ($r=0.30$, $p\leq0.05$)(19), fatigue ($r=0.45$, $p<0.001$)(20), insomnia ($r=0.27$, $p=0.006$)(21) and dyspnoea ($r=0.26$, $p\leq0.05$)(22).

Only one of the previous mentioned studies determined symptom associations with pain in the population of elderly, but they received hospice care (19). The associations found could differ from the population of independently living frail elderly in palliative care due to age-related decline, comorbidities and high mortality. A lack of evidence exists regarding a prediction model for pain in independently living frail elderly in palliative care. Predicting pain by determining associations with other symptoms may help to gain earlier identification of pain. Thereby opening up the possibility to earlier discuss adequate pain management within advanced care planning with the patient and/or loved ones, including non-pharmacological and pharmacological interventions.

Aim

The aim was to determine whether the symptoms anxiety, fatigue, loss of appetite, insomnia, and dyspnoea are predictors for pain in independently living frail elderly in palliative care and to develop a prediction model.

Method

This cross-sectional study assessed predicting variables and outcome variable simultaneously for each patient. The study was carried out with patients from multiple community-care organisations in the Netherlands from February until May 2021.

Population and Domain

A purposive sampling was used to include eligible patients for this study. These eligibility criteria were: having a life expectancy of less than one year, is 65 years or older, living at home, having assistance from home-care nursing, is screened frail (total score ≥ 4) based on the Groningen Frailty Indicator (GFI)-questionnaire and is able to self-assess and communicate their symptoms (23). The life expectancy was determined by the community-care nurses based on the 'surprise question': "Would I be surprised if this patient were to die

in the next twelve months?" (24). The surprise question is highly effective in predicting patients in high need for palliative care (24). To ensure reliability on the symptom intensity scores, patients were excluded when they had a diagnosis of dementia or mild cognitive impairment.

Data collection

To determine which symptoms are predictors for pain, the Utrecht Symptom Diary (USD) was used to assess intensity of predicting symptoms and outcome variable pain (25). This is a validated Dutch-translated and adapted version of the Edmonton Symptom Assessment System (ESAS) to self-assess the eleven most prevalent symptoms and overall well-being in cancer patients (25). Patients self-assessing their symptoms is considered the "gold standard" for symptom assessment (26). The severity of symptoms at the time of assessment were rated from zero to ten on a Numerical Rating Scale (NRS), in which zero means that the symptom was absent and ten that it was of the worst possible severity (26). Covariables were collected on the Case Report Form (CRF). According to the rule of thumb by Peduzzi stating ten cases per explanatory variable, sample size was set at 80 patients based on five predicting symptoms and three selected covariables (27). Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Checklist for prediction model development was used to facilitate reporting of the results (28).

Procedures

Multiple community-care nurses from different organisations assisted in the data collection. Through networking efforts they voluntarily were willing to help with the data collection for this study. The community-care nurse checked eligibility of patients with the use of the study protocol, tutorial-video from the main researcher or in a meeting with the main researcher(anonymously). The community-care nurse asked the eligible patients to participate and provided study information, after which informed consent was signed.

Data was collected on the hard-copy questionnaires CRF and USD. CRF was completed by the community-care nurses with help of the patient and USD was completed by the patients. When patients were unable to write down their answers but able to read the USD and verbally communicate their answers, nurses assisted in circling the answer. Collected data per patient was sent to the main researcher by secure email. Before entering collected data into the database, a participant identification-number was granted by the main researcher to each case. By participant ID-number data would be anonymously traceable to the data of each individual case.

Monthly reminders were sent out to the participating community-care nurses to regain focus on the study, to include patients, collect data and provide updated information on missing data and response-rate.

Data analysis

In order to state results of which present symptom predicts presence of pain, symptom scores were dichotomized. Scores on the five predicting symptoms and outcome variable were dichotomized in absence (score = 0) or presence of a symptom (score = 1). Symptom scores equal and greater than three were regarded as clinically relevant (25). Covariables (age, sex and living situation) were selected based on known relevance (29-31). Missing data patterns were explored. Multiple imputations was enquired when equal or higher than ten percent data of the complete dataset was missing, otherwise mean imputations was employed. If missing data in the dataset was less than five percent, it was considered inconsequential (32).

A multivariable logistic regression model was created with the dichotomized USD pain score as outcome variable and dichotomized symptom scores anxiety, fatigue, loss of appetite, insomnia, and dyspnoea as predictor variables. The symptoms and covariables were added using backward selection procedure. Influential outlier cases were checked with Cook's distance and (multi)collinearity was considered by assessing Variance Inflation Factor (VIF) for each individual predictor variable.

To determine predictive accuracy of the final model, the Receiver Operating Characteristics (ROC)-analysis was used to determine Area Under the ROC Curve (AUC). AUC of ≥0.80 indicated good accuracy and fair accuracy is described with an AUC between 0.70 and 0.80 (33). Sensitivity and specificity were estimated with cross-tabulation. Statistical significance (two-sided) was set at $p \leq 0.05$. All analyses were conducted using 'Statistical Package for the Social Sciences' (SPSS) version 23.0 (34).

Ethical Issues

A non-WMO (the Medical Research Involving Human Subject Act) statement was granted by the Ethics Committee of the University Medical Centre Groningen [registration number: 202100021](35). Patients provided written consent to use their collected data for scientific purposes. Regulations of the General Data Protection Regulation (in Dutch: Algemene Verordering Gegevensbescherming (AVG)) were followed (36). The study was conducted according to the Declaration of Helsinki (latest version WMA General Assembly 2013) (37).

Results

Participants

In total, 83 patients were enrolled in this study. Of these patients, 39.8% were men and the mean age was 84.2 (range 66 – 100 years). The living situations of the patients were: 67.5% lived alone and 28.9% lived with a partner or loved one. Disease of the cardiovascular system was the most common primary diagnosis. The mean frailty score was 7.7 (maximum GFI-score is 15). Generally the respondents had the availability of an informal caregiver. Patient characteristics are presented in Table 1.

(Position of Table 1 in the text)

Prevalence and intensity of selected symptoms

Table 2 presents the prevalence and intensity of selected symptoms. The prevalence of pain was 56.6% with a mean intensity score of 3.5. Most uncommon symptom was anxiety: 26.5% with a score of one or higher, and 22.9% with a score of ≥ 3. Most prevalent symptom was fatigue (83.1%) and had the highest mean intensity score (score = 5.3).

(Position of Table 2 in the text)

Specification of modelling

Of all datapoints, 0.66% were missing and thereby data was not imputed. Missing values on the explanatory variables were recoded in SPSS as system missing value. Thereby including all available cases in further analysis (N=83). Developing the model with multivariable logistic regression presented the presence of dyspnoea (B=1.458, SE=0.486, OR=4.299, 95% CI; 1.658 to 11.148, p=0.030) as an independent predicting symptom for pain after correction for age, sex and living situation. Sex(female) was a significant predicting covariable (B=0.980, SE=0.493, OR=2.665, 95% CI; 1.014 to 7.004, p=0.047). After computing Cook's distance zero cases were found to have an undue influence on the regression line (Cook's distance range 0.00 - 0.06). All cases were found to be a representative case of the population and therefore were included in the analysis. Assessment of (multi)collinearity determined that no variables were collinear (VIF range 1.0-1.3). Specifications of the final model are presented in Table 3.

(Position of Table 3 in the text)

Model performance

The final model resulted in 24 true negative, 15 false negative, twelve false positive and 32 true positive predictions of presence of pain. The overall percentage of correct predictions was 67.5%. The AUC was calculated at 0.723 (95% CI; 0.610 to 0.836, p=0.001). Cross-tabulation, as presented in Table 4, gave a sensitivity of 0.681 and a specificity of 0.667. Thus, in the final model, with sex(female) and presence of dyspnoea as significant predictors, approximately 68.1% of independently living frail elderly in palliative care would be correctly identified as experiencing pain, and 66.7% would be correctly identified as not experiencing pain. Figure 1 illustrates the results of the model performance using a ROC-curve.

(Position of Table 4 in the text)

(Position of Figure 1 in the text)

Discussion

This study was conducted to give insight into the symptoms anxiety, fatigue, loss of appetite, insomnia, and dyspnoea as predictors for experiencing pain in independently living frail elderly in palliative care. This study found that dyspnoea was an independent predicting symptom for pain and added sex(female) as significant covariable in the final model. The AUC of 0.723 succeeded to have fair predictive accuracy. The estimated Odds Ratio of presence of dyspnoea indicated that patients experiencing dyspnoea have a 4.299 times higher chance of experiencing pain than patients who are not experiencing dyspnoea. The estimated Odds Ratio of sex(female) indicated that patients who are female have a 2.665 times higher chance of experiencing pain than patients who are men.

More than half of the population in this study recorded presence of pain (56.6%). This was found to be in comparison with other studies of pain experienced in independently living elderly with a life expectancy of less than one year (38-39). In a study with older community residents the prevalence of experiencing pain one year prior to death was set at 37% up to 66% one month prior to death (38). An overview of other studies including elderly people with a life expectancy of less than one year, showed that prevalence ranged from 57% up to 88% (39). Freeman et al. showed a prevalence of dyspnoea of 44.9% in community-dwelling palliative home care patients (40). This is similar to the prevalence of dyspnoea in this study. Dyspnoea was an independent predictor for pain with a prevalence of 53%. The perception of dyspnoea shares similarities with the perception of pain. The cortical processing of dyspnoea and pain might explain the similarities, because it is commonly involved in processing of potentially distressing interoceptive stimuli (41-42). Associations were found

between higher unpleasantness of perceived dyspnoea and higher unpleasantness of perceived pain (41).

The final model showed sex(female) as a significant covariable for prediction of pain. Women might be at higher risk for many common pain conditions in comparison with men (43). Biological factors, such as sex hormones, are thought to explain sex differences in pain perception. Sex hormones appear to regulate the cortical processing of pain-related stimuli (43).

Strengths and Limitations

A strength of this study was that the analysis was run on a near complete dataset. Less than one percent of all datapoints (eleven of 1660 datapoints) were missing and of the explanatory variables in the model four of 664 datapoints were missing (0.6%). These datapoints were on variables 'living situation', 'USD score on fatigue' and 'USD score on well-being', and were considered to be missing completely at random. Another strength of this study was that the parameters of the outcome variable were equally distributed with prevalence of presence of pain at 56.6%. This accommodated in having discriminative abilities in the development of the final model.

This study also had some limitations. Selection bias may have occurred during the start of data collection due to the use of the surprise question as method for marking the palliative phase. This was a new method for most participating nurses. Terminally ill (life expectancy < 6 months) or end-stage diseases were easier for them to identify and experiencing pain might have been overestimated in the population. After one month of data collection, a tutorial video was send with an explanation on the application of the inclusion criteria for this study. The predictors of the final model had wide confidence intervals of the Odds Ratios, resulting in less certain set conclusions. Also the developed prediction model had low sensitivity (0.681) and low specificity (0.667), resulting in less true positive rates (proportion of positives correctly identified) and lower true negative rates (proportion of negatives correctly identified). This might be due to a smaller sample size used for prediction modelling. Instead of ten cases per explanatory variable, ten Events per Predictor Parameter (EPP) could be chosen as rule of thumb to increase calculated sample size (44). According to EPP, sample size of this study would then be calculated at N=150.

Implications

This study showed the first prediction model for the presence of pain in independently living frail elderly in palliative care. It showed that signalling presence of dyspnoea and female-sex can be part of predicting the presence of pain. Early identification of pain through

its predictors can help community-care nurses in discussing adequate pain management earlier with the independently living frail elderly.

In daily practice community-care nurses need to asses symptom burden and monitor symptoms over time. With the knowledge that elderly patients underreport their pain (e.g. due to age-normative beliefs) and knowing by this prediction model that presence of dyspnoea and female-sex are predictors for experiencing pain in independently living frail elderly in palliative care, nurses can intensify monitoring for pain. It can also trigger community-care nurses to think about the condition of the patient with regards to pain-related suffering and to use this awareness while planning and providing palliative care. Within advanced care planning they can discuss forms of interventions to deal with pain, such as complementary therapies or pain medication, to tailor care to the wishes of the patients and/or loved ones. This model was built based on the population of independently living frail elderly with a life expectancy of less than one year. In this stage in life it is, for the most part, still possible to communicate with patients and/or loves ones about advanced care planning and to tailor care to a patients' final wishes. It may result in lowering the degree of unnecessary suffering of pain in independently living frail elderly at the end of their lives.

The model was built on known covariables and the presence of predicting symptoms with a symptom intensity ranging from one to ten. Clinically relevant symptoms of the USD have an optimal cut-off point of equal and higher than three. A recommendation for future research is to analyse if the selected symptoms are independent predictors for pain when assessed as clinically relevant symptoms. Future prediction modelling studies to this topic need to be undertaken with a larger sample size to sustain conclusions with regards to the models' performance.

Conclusions

This study showed presence of dyspnoea as an independent predictor for the presence of pain in independently living frail elderly with a life expectancy of less than one year. The final prediction model presented sex(female) as a significant covariable and had succeeded to have fair predictive accuracy with an AUC of 0.723.

Therefore the prediction model developed in this study could be used by community-care nurses to identify presence of pain through signalling of presence of dyspnoea and female-sex, and thereby enable earlier discussion and provision of adequate pain management with the patient and/or loved ones.

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Tables and Figures

Table 1. *Patient characteristics of the Respondents (N=83)*

Characteristic	Values
Sex[male], N (%)	39.8%
Age in years, mean ± SD	84.2 ± 8.5
Score on Groningen Frailty Indicator, mean ± SD	7.7 ± 2.7
Living situation, N (%)	Alone 56 (67.5%) With a significant other 22 (26.5%) With other loved ones 2 (2.4%)*
Availability informal caregiver, N (%)	Non-residential informal caregiver 49 (59%) Living with an informal caregiver 20 (24.1%) Not available 14 (16.9%)
Primary diagnosis, N (%)	
- Disease of cardiovascular system	28 (33.7%)
- Disease of nervous- and sensory system	14 (16.9%)
- Disease of respiratory system	14 (16.9%)
- Disease of digestive system	5 (6%)
- Cancer	12 (14.5%)
Primary cancer site	Urological 5 (6%) Gastrointestinal 2 (2.4%) Brain 2 (2.4%) Gynaecological 1 (1.2%) Skin 1 (1.2%) Other primary cancer site 1 (1.2%)
- Other primary diagnosis	10 (12%)
Use of pain medication[yes], N (%)	56 (67.5%)
Type of pain medication, N (%)	Non-opioids 41 (49.4%) Opioids 7 (8.4%) Both 8 (19.6%)

*Add up error due to missing value on 3 cases (3.6%)

Table 2. *Prevalence and Intensity of selected symptoms (N=83)*

Symptoms	Mean (SD)	Median	USD* ≥ 1 N(%)	USD* ≥ 3 N(%)
Pain	3.5 ± 3.5	3.0	47 (56.6%)	43 (51.8%)
Insomnia	3.2 ± 3.3	2.0	47 (56.6%)	41 (49.4%)
Loss of appetite	2.7 ± 3.1	1.0	46 (55.4%)	35 (42.2%)
Dyspnoea	2.9 ± 3.3	1.0	44 (53.0%)	38 (45.8%)
Fatigue	5.3 ± 3.2	6.0	69 (83.1%)	63 (75.9%)
Anxiety	1.4 ± 2.6	0.0	22 (26.5%)	19 (22.9%)

*USD is an abbreviation of Utrecht Symptom Diary

Table 3. *Predictive score – Equation of the model*

Variables	Regression coefficient B	Standard error	Wald	*p*-value	Exp(B)	95% Confidence interval for Exp(B)	
						lowest	highest
Dyspnoea(presence =1) , *x1*	1.458	0.486	8.999	0.030	4.299	1.658	11.148
Sex(female=1), *x2*	0.980	0.493	3.952	0.047	2.665	1.014	7.004
Constant	-1.053	0.458	5.277	0.022	0.349		
Equation: presence of pain = -1.053 + 1.458·x1 + 0.980·x2 (Nagelkerkes R^2:0.21)							

Table 4. *Accuracy of the Final Multivariable Model*

	Total, N	Pain, N	No pain, N	Sensitivity, % (95% CI*)	Specificity, % (95% CI*)	PPV[a], % (95% CI*)	NPV[b], % (95% CI*)
Predicting pain, N	44	32	12	32/47 = 68.1% (52.9-80.9%)	24/36 = 66.7% (49-81.4%)	32/44 = 72.7% (61.8-81.5%)	24/39 = 61.5% (49.8-72.1%)
Predicting no pain, N	39	15	24				
Total, N	83	47	36				

Sensitivity: ability to correctly identify patients who are experiencing pain, Specificity: ability to correctly identify patients who are not experiencing pain
[a]PPV = Positive predictive value: ability to predict experiencing pain, [b]NPV = Negative predictive value: ability to predict not experiencing pain
*CI: Confidence Interval

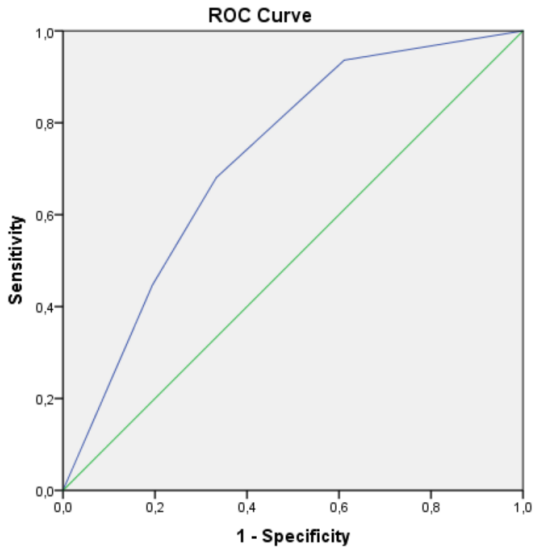

Figure 1. *Receiver under the Operator Curve(ROC)-curve of the Final Multivariable Logistic Regression model (Area Under the ROC-Curve of 0.723, p=0.001)*