

Maximizing Acceptance of Clinical Pharmacy Recommendations May Reduce The Length of Hospital Stay in A Private Hospital From Amman, Jordan: Toward Fully Independent Pharmacist Prescribers

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Abstract

Background: Clinical pharmacy interventions (CPI) usually require prior medical authorization with 20% being rejected. If pharmacists prove to be more competent in this area (accept 100% of CPI), the profession will step closer to a fully-independent prescriber status.

Objective: This study use an artificial neural network (ANN) model to determine whether clinical pharmacy (CP) may improve outcomes associated with rejected CPI.

Setting: This is a non-interventional, retrospective analysis of documented CPI in a 100-bed, acute-care private hospital in Amman, Jordan.

Method: Study consists of 542 patients, 574 admissions, and 1694 CPI. Team collected demographic and clinical data using a standardized tool. Input consisted of 54 variables with some taking merely repetitive values for each CPI in a given patient whereas others varying with every CPI. Therefore, CPI was consolidated to one rejected and/or one accepted per patient per admission. Groups of accepted and rejected CPI were compared with matched and unmatched variables. ANN were, subsequently, trained and internally as well as cross validated for outcomes of interest. Outcomes were length of hospital and intensive care stay after the index CPI (LOSTA & LOSICUA, respectively), readmissions, mortality, and cost of hospitalization. Best models were finally used to compare the two scenarios of approving 80% versus 100% of CPI. Variable impacts (VI) automatically generated by the ANN were compared to evaluate the effect of rejecting CPI.

Main outcome measure: Lengths of hospital stay after the index CPI (LOSTA).

Results: ANN configurations converged within 18 seconds and 300 trials. All models showed a significant reduction in LOSTA with 100% versus 80% accepted CPI of about 0.4 days (2.6 ± 3.4 , median (range) of 2 (0 – 28) versus 3.0 ± 3.8 , 2 (0 – 30), P-value = 0.022). Average savings with acceptance of those rejected CPI was 55 JD (~ 78 US dollars) and could help hire about 1.3 extra clinical pharmacist full-time equivalents.

Conclusion: Maximizing acceptance of CPI reduces the length of hospital stay in this model. Pharmacists seem to be well-positioned to target gain the upper hand on prescribing in these situations.

Impact Of Findings On Practice Statement

- For the first time, pharmacists and healthcare providers have evidence that rejected interventions may in fact be better approved.
- This study supports more pharmacist prescribing privilege
- This is a first step in building a more medically-integrated pharmacy practice
- Pharmacy practice setting is a major factor in determining benefit of approving rejected interventions and must be considered in future research.

Background

Clinical pharmacist interventions (CPI) reduced length of stay in various settings (1) (2). Additionally, they shortened intensive care and hospital resource utilization (3). Researchers further showed a significant improvement in survival with CPI (4) (5). Moreover, they have enormous financial benefits to payers (6) (7) (8) (9). In contrast, CPI had conflicting effects on reducing readmissions (10) (11) (12) (13). Impact on the duration of hospitalization seemed negligible in a Scandinavian emergency department as well (14). Therefore, the effect of CPI may vary among institutions.

Now, CPI usually requires prior authorization of a physician and hence is associated with acceptance rates in the range of 80% (15) (16). Several factors garner higher acceptance including class of medications and CPI, diseases and specialties of physicians, as well as experiential background of clinical pharmacists (16) (17). On the other hand, despite resistance to pharmacist prescribing, more evidence is building up as to its value for patient care (18) (19). Therefore, it is of primary importance to reconcile the 20% disagreement on pharmacotherapy that exists between pharmacists and physicians. Up to this point, scarcely, if at all, does the literature evaluate this due to the many variables involved and extreme difficulty in conducting such an experiment.

Artificial neural networks (ANN) are a very powerful tool that we use to resolve complex doubts by analyzing real usual care data (20). These models evade the need to rigorously intervene and, hence, make sophisticated protocols of blinding and randomization of patients often unnecessary (20).

Aim of the Study

In this study, we use ANN to evaluate the outcomes associated with maximizing the acceptance of CPI from 80% to almost 100% and hence whether pharmacists qualify for a full independent prescribing authority. Specifically, would accepting more CPI potentially improve healthcare outcomes such as length of hospital and intensive care stay, reduce readmissions, improve survival, or reduce costs?

Ethics Approval:

Authors obtained local ethics approval number 2020-PHA-8.

Methods

Primary Outcome: Length of hospital stays after the index CPI (LOSTA) as a continuous variable.

Secondary Objectives: Length of Intensive care unit (ICU) stays after the index intervention (LOSICUA) and cost of hospitalization (both continuous) as well as readmissions and mortality (both categorical).

Study Institution and Setting: A 100-bed, tertiary- and acute-care private hospital.

Clinical Pharmacy Team: Three clinical pharmacists with 4, 7 and 8 years of clinical pharmacy experience. All are doctor of pharmacy or master of clinical pharmacy certificate holders. Clinical pharmacist with the shortest experience was also a recent hire.

Study Design: Usual care, eight-month-long, two-phase, non-interventional study.

Study Subjects: Inclusion and Exclusion criteria

Consecutive patients of all ages were included when admitted to the study institution with CPI to outpatients excluded due to the unavailability of outcomes.

Data Collection

Team documented daily usual recommendations using a standardized Microsoft Excel 2010 tool (version 14.0.4374.1000). Variables documented for each CPI can be found in Tables 1 (matched between accepted and rejected CPI) and 2 (unmatched). In the study database each row constituted a CPI. For each patient, there were multiple CPI in a given admission and patients may have been admitted more than once during the study period. Hence, for each patient during a given admission, some variables value may have been merely a repetition with every CPI allowing us to use that value in a consolidated CPI. Other variables varied with every CPI. Therefore, we consolidated the data to a maximum of one accepted and one rejected per patient per admission using arbitrary ordinal scores for the variables changing with every CPI. These scores were calculated with the details provided in the definitions subsection. Medication information from the local pharmacy and stock management databases were confirmed. Similarly, the laboratory information from the local laboratory database was reported. Lengths of hospitalization, readmissions, and costs were collected from the local admissions database. All these databases were built by Microsoft Access 2000 (version 9.0.6926 SP-3) and managed by the information technology (IT) department in the hospital. Status of the patient upon discharge, whether alive or deceased, was provided by the IT department.

Definitions

Phase I, from January 1st to March 31st, 2019, was a pilot to estimate the needed sample size. Phase II, was conducted from April 1st to August 31st, 2019. Again, Table 1 (36 matched variables) and Table 2 (18 unmatched) summarize all the 54 variables included in this model. As the reader may appreciate, some of these were continuous like age in years, total number of CPI, or the length of hospital or intensive care stay before the first index CPI in days (LOSBI and LOSICUBI). However, the majority were categorical. For example, in Table 1, our reader can see that some CPI was made in critical cases in the intensive care unit whereas others made in non-critical medical cases. Most categorical variables are listed such that a given factor is either present (Yes) or absent (No). For example, there were 55 CPI (11%) in the accepted group and 20 CPI (12%) in the rejected group on beta blocker medications. Obviously, beta blockers were matched between accepted and rejected CPI groups. Poly-pharmacy was a dichotomous variable with 1

for ≥ 8 regular medications and 0 otherwise. Previously published literature was used to identify medication and disease-related variables predicting hospitalization due to drug adverse effects (21).

Non-green antibiotics are a special traffic signal classification we use in antimicrobial stewardship programs. For example, meropenem is red, cefepime is orange, and levofloxacin is green. Red antibiotics are the most serious and require rigorous stewardship while green antibiotics undergo only limited control.

After a quick revision of all types of recommendations made, it was found that there were significant differences between safety and efficacy CPI, i.e. those made to prevent an adverse effect and those made to improve the efficacy of a treatment.

Another area of difference was between orders made to add or stop a medication. Differences were absent or little for the other types, and therefore, these were grouped under miscellaneous. Unreported or difficult to categorize CPI were grouped under "Not determined".

Scores were calculated to consolidate all CPI to a maximum of 1 accepted and/or rejected per patient per admission. These scores took a value between 0 and 1. For example, CPI was considered complex (took the value of '1') if it involved putting two or more pieces of information together. Simple CPI (took a value of '0') if based on one direct piece of information; for example, if the patient was hypotensive, the simple CPI was to stop the antihypertensive drug. Follow-up CPI (took a value of '0.5') would be based on a check of a new investigation and hence follow-up on a previous CPI. Therefore, problem complexity score is a total average % of all; complex, simple, and follow-up CPI made for a given patient during an admission. As the reader may see, the two groups were comparable in the complexity of CPI (1 versus 0.9 for accepted and rejected CPI groups, respectively, and ranges in brackets). Similarly, Problem intention score is a total % average of errors and problems documented for a given patient during the admission. CPI is a problem (took a value of '1') if the physician tried to defend their original plan. It was an error (took a value of '0') if the physician immediately agreed or explicitly clarified that they made a mistake. Clinical domain score is a % average of clinical (value of 1) versus operational (value of 0) CPI for that admission. An example of a clinical CPI is changing a dose. Whereas an example of operational CPI is to reuse a given stable intravenous medication vial for multiple doses. Clinical Prescribing step score is a % average of CPI for that admission made to the prescribing step in the medication use process. The consultancy score is a % average of the clinician approaching the clinical pharmacist (value of '1') versus the clinical pharmacist approaches the clinician (value of '0') during that admission. Outcomes driven score is a % average of CPI made based on outcomes versus those made with guidelines for that admission. Rejection score is % of CPI rejected in that admission. Combined clinical pharmacy (CP) success score is the % average of clinical pharmacist's successful CPI averaged over that admission. The physician rejection score is the % of physicians' rejection rates during the whole study period averaged for that admission recommendations. The diagnosis revision score is the % of all diagnoses that were revised or changed by the end of the admission. The acceptance or rejection of the CPI was entered as a dichotomous input variable.

Finally, outcomes studied were LOSTA, length of stay in the intensive care unit (LOSICU), LOSICUA, readmission, mortality, and cost of admission.

Data Analysis

Analysts consolidated the data for a total of one CPI in accepted or rejected groups per admission per patient. Variables for different CPI were simply set to the matching values or calculated scores described in the definitions section. Final inclusion and refinement of scenarios are presented in Figure 1. Our reader can see that a total of 1694 CPI was finally consolidated to 684 CPI, 519 in the accepted and 165 in the rejected groups, respectively. Univariate analyses were conducted to compare the rejected and accepted CPI groups (Table 1 and Table 2). Finally, the research team built, trained, tested, and cross validated ANN for the main and various outcomes.

Statistical Analysis

The data was analyzed using Stat Tool, version 6.3.0 (Palisades Corp) to generate P-values using Mann Whitney U Test unpaired groups for continuous data, Chi-squared (χ^2) test for categorical variables, McNemar Test for categorical outcomes during re-assignment ANN analyses, Wilcoxon Mann Whitney Test for continuous paired outcomes during re-assignment.

ANN Model

Inputs included 54 variables, either matched (36 in Table 1) or unmatched (18 in Table 2), per patient. Diagnoses were made by clinicians and documented in the study form. An ANN model (Figure 2) was developed using NeuralTools, version 7.6.0 (Palisade Corp., Ithaca, NY). This is a fully connected feed forward ANN. Just like in our former studies, the first hidden layer (1 per training CPI) ensures accurate performance (20). The second hidden layer (2 neurons, one nominator and one denominator) reduces dimensionality to drive ANN toward fast convergence (i.e., an optimal solution that can be reliably used to predict outcomes) (20). Input layer consist of one neuron for each input variable. This would be 54 for the total or just 18 if only unmatched variables are included. An additional categorical input neuron may be added for the status of CPI accepted versus rejected. Cross validation set consisted of random 4 scenarios after initial training (544, 80%) and testing (136, 20%). Sensitivity report figures showed that this distribution of training, testing and cross validation resulted in no over fitting (available upon request). Reassignment and live predictions enabled the study of effect of maximizing acceptance of CPI from 80% to 100%. In addition, model automatically generated variable impacts (VI), an overall % contribution of a given variable to predict outcome. These were simply compared for all variables.

Sample Size Calculation

Authors used The University of California, San Francisco (UCSF) sample size calculator site (URL: <http://www.sample-size.net/sample-size-study-paired-t-test/>, Accessed November 27, 2019). Using Phase I data, a standard deviation of change with 80% acceptance versus 100% acceptance of CPI of 1.05 was

used. At two-tailed-alpha of 5% and power 80%, a sample size of 554 consolidated CPI to detect an effect size of about 3 hours (0.125 days) difference in LOSTA was needed.

ANN model for the matched variables would expertly need $19 \times 10 \times 2 = 380$ sample size. But for a larger ANN including unmatched variables the sample needed would go up to $54 \times 10 \times 2 = 1080$.

Results

Factors associated with Rejection of CPI

Critical care, pediatric age group, and non-green antibiotics were statistically matched between the two groups of accepted and rejected CPI (Table 1). We have no oncology cases and hence this specialty may not be compared between the two groups. Generally, for most mismatched variables (Table 2), there were more such variables in the rejected group. For example, stopping (42% versus 26%, P-value < 0.001) or adding (29% versus 21%, P-value = 0.027) medications were both associated with higher rejections of CPI. Clinical pharmacists with greater experience of 7 or 8 years were more likely to intervene successfully (95% and 86% versus 57%). Respectively, these clinical pharmacists had 147, 452, and 824 successful CPI out of 256, 475, and 963 made (χ^2 P-value = <0.001). In total, our clinical pharmacists made 1423 successful out of 1694 CPI (84%). In Phase II, there were fewer rejections probably due to the clinical pharmacist with the least experience contributing fewer CPI in this phase. Generally, on a detailed analysis of every intervention made, the study panel agreed on the vast majority (> 99%) of CPI, both accepted and rejected, with the clinical pharmacist rather than the physician. This is an expert judgment rather than an assumption and has no effect on the ANN model predictions.

ANN Model Convergence and LOSTA outcome

ANN model converged within 18 seconds and 270 training cycles. Cross validation was very close to identity curve with accurate predictions in all models (e.g. LOSTA ANN $R^2 = 0.9923$). Variable Impacts only for important factors are shown in Figure 3. Rejection of CPI (combined VI of about 10%; namely 6.5% for physician rejection rate and 4% for combined CP success score) is a significant predictor of LOSTA. In this ANN model, 100% versus 80% accepted CPI were associated with 0.4 days less of hospital stay after the index CPI (2.6 ± 3.4 , median (range) of 2 (0 – 28) versus 3.0 ± 3.8 , 2 (0 – 30), P-value = 0.022). Including only the 19 variables mismatched in the univariate analysis (i.e. the 18 in Table 1 plus the dichotomization binary code of accepted and rejected CPI), the ANN model converged within 3 seconds and 110 training cycles. Exactly the same cross validation results and LOSTA differences were observed with 100% versus 80% acceptance of CPI (2.6 ± 3.4 , median (range) of 2 (0 – 28) versus 3.0 ± 3.8 , 2 (0 – 30), P-value = 0.022). However, the number of CPI as well as the measure of their acceptance emerged as the major determinant of the LOSTA outcome. Physician rejection rate, combined CP success score, and rejection score overall explains about 28% of the variability in LOSTA (Figure 4).

Secondary Outcomes

All secondary outcomes were insignificantly reduced with LOISCUA 0.4 ± 1.7 with median (range) of 0 (0 – 16) versus 0.5 ± 1.7 with 0 (0 – 16) (P-value = 0.693). Readmissions (99 out of 684) for both scenarios and 8 cases each switching to the opposite readmission category. Mortality was 1.2% versus 1.9%, P-value = 0.131, with only 6 and 1 cases shifting mortality status. Cost of hospitalization was reduced by a statistically insignificant average of 55 JD per consolidated CPI (2116 ± 2837 versus 2171 ± 2864 , P value = 0.721).

Discussion

To the best of our knowledge, this study is the first to demonstrate using an ANN model that maximizing acceptance of CPI reduces the length of hospital stay and saves hospitalization costs.

Factors that predispose a CPI to be rejected seem to vary with the setting. For example, critical care, pediatric age group, anti-infective medications, and oncology drugs are four areas with significantly higher acceptance rates of CPI in our previous governmental study (16). In this acute care private setting, however, difference in the acceptance rates in these specialties was insignificant. Moreover, stopping a medication was more likely to be accepted in the former whereas associated with higher rates of rejections in the latter (16). Adding a drug was more likely to be rejected in both studies. Hence, albeit unscientific, physician's decision to accept or reject a CPI may be partially driven by practice perspective.

Somers et al evaluated clinical pharmacy recommendations in a geriatric population (22). They found that when physicians accepted about 54% of CPI, a panel of four physicians, pharmacologists, and clinical pharmacists accepted above 85%. Similarly, in our acute care setting, the overall acceptance rate of 84% by physicians, in fact had to be around 99% according to our researcher's panel detailed review. These acceptance rates are consistent with other studies in the acute care setting, which were found to be in the range of 76 to 93% (23) (24) (25) (26). However, the clinical implications of these opposing pharmacotherapy decisions remain to be assessed. Expert judgment in this study support maximizing the acceptance of CPI but has no effect on the ANN model itself. Therefore, both our study expert panel and the results of the ANN model are concordant in anticipating better outcomes with opting to a pharmacist upper hand on prescribing upon dealing with a rejected CPI.

Redmond et al have shown in a Cochrane meta-analysis of 20 pooled randomized clinical trials that CPI effects on secondary outcomes, including healthcare utilization, were of little certainty (27). Similarly, our study shows that rejecting CPI has an insignificant effect on the secondary outcomes of LOSICUA and mortality. However, there was a consistent prolongation of hospitalization by about one shift or 0.4 days with these rejections. On average, the extra cost of a rejected CPI would be around 55 JD. For the study site, this would be sufficient to hire 1.27 full-time equivalents (FTE) of a clinical pharmacist. In conclusion, all three factors; namely the expert assessment, LOSTA, and cost point in the same direction in support of a 100% approval of CPI.

Limitation of this study is being the first retrospective in this field. However, three separate factors support our conclusion and further research in different practice settings may prospectively confirm its findings.

Conclusion

ANN models show that maximizing acceptance of CPI reduces LOSTA and saves costs while expert judgment supports this notion in parallel. Clinicians and society will most likely benefit from promoting CP to full prescriber status. Caution should be exercised as these findings are not one-size-fit-all and may vary with setting.

Abbreviations

ANN Artificial Neural Networks

CP Clinical Pharmacy

CPI Clinical Pharmacy Interventions

ICU Intensive Care Unit

IT Information Technology

LOSBI Length of hospital stay before the index clinical pharmacy intervention

LOSTA Length of hospital stay after the index clinical pharmacy intervention

LOSICU Length of stay in the intensive care unit

LOSICUA Length of stay in the intensive care unit after the index clinical pharmacy intervention

LOSICUBI Length of stay in the intensive care unit before the index clinical pharmacy intervention

VI Variable impact (see methods under ANN model subsection for definition)

Declarations

Ethics approval and consent to participate We had local Institutional Review Board approval number 2020-PHA-8 (available upon request).

Consent to Publish We had local Institutional Review Board approval number 2020-PHA-8 (available upon request).

Availability of Data Materials Data used in this study are available EXCEL spreadsheet format from the corresponding author to any researcher/scientist upon request

Competing interests All authors have no competing interests to disclose

Conflicts of Interest: All authors have no conflicts of interests to disclose for this research.

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Authors Contributions: Author **LMS** is the primary author, conceptualized work, collected and analyzed data. **AHK, SAS,** and **IAB,** all had major input to conceptualization, analysis and revision of this study.

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Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

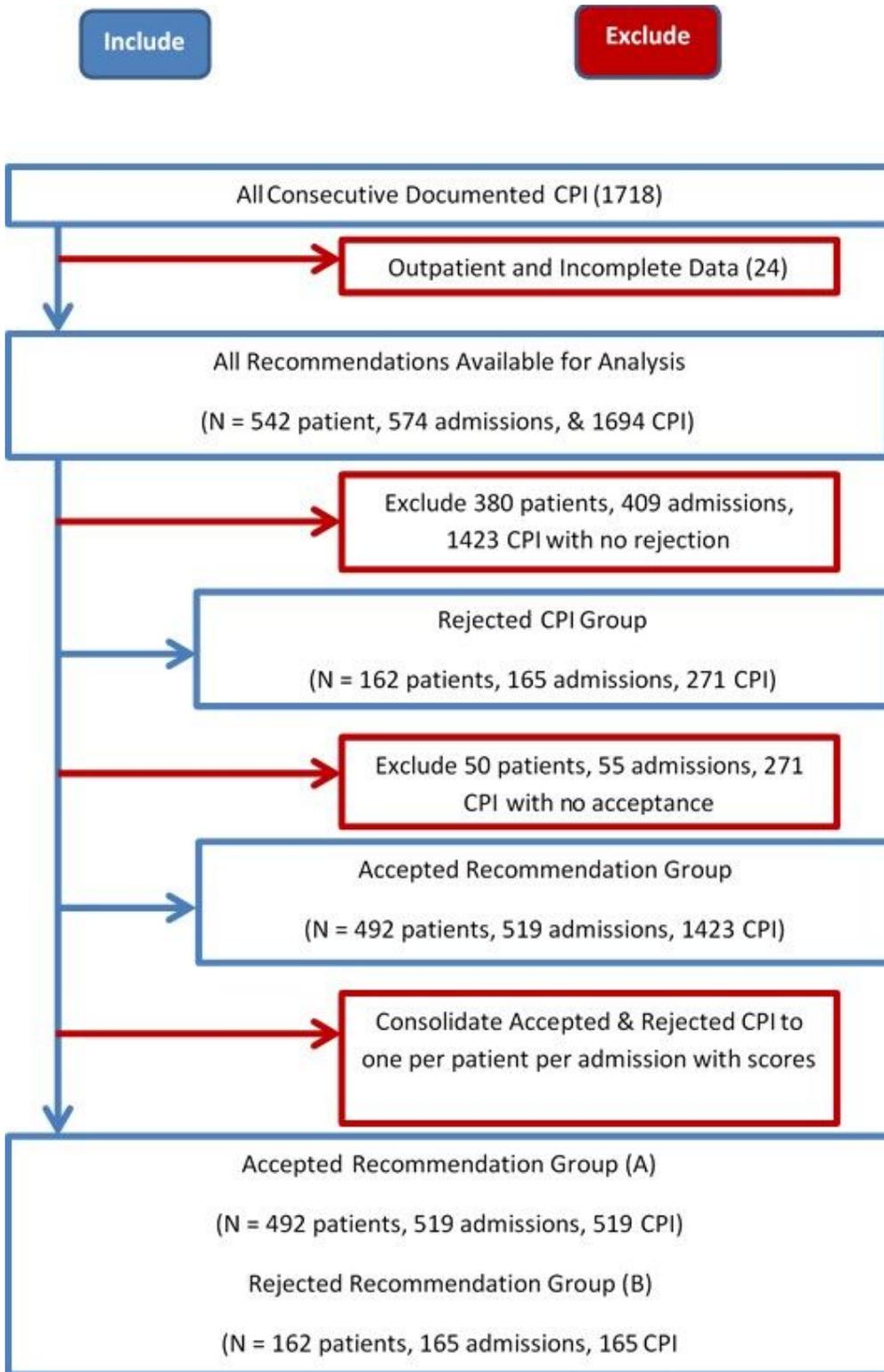


Figure 1

Summary of Inclusion of All Consecutive Patients with Documented Recommendation until final consolidation into one accepted and/or one rejected recommendation per patient per admission.

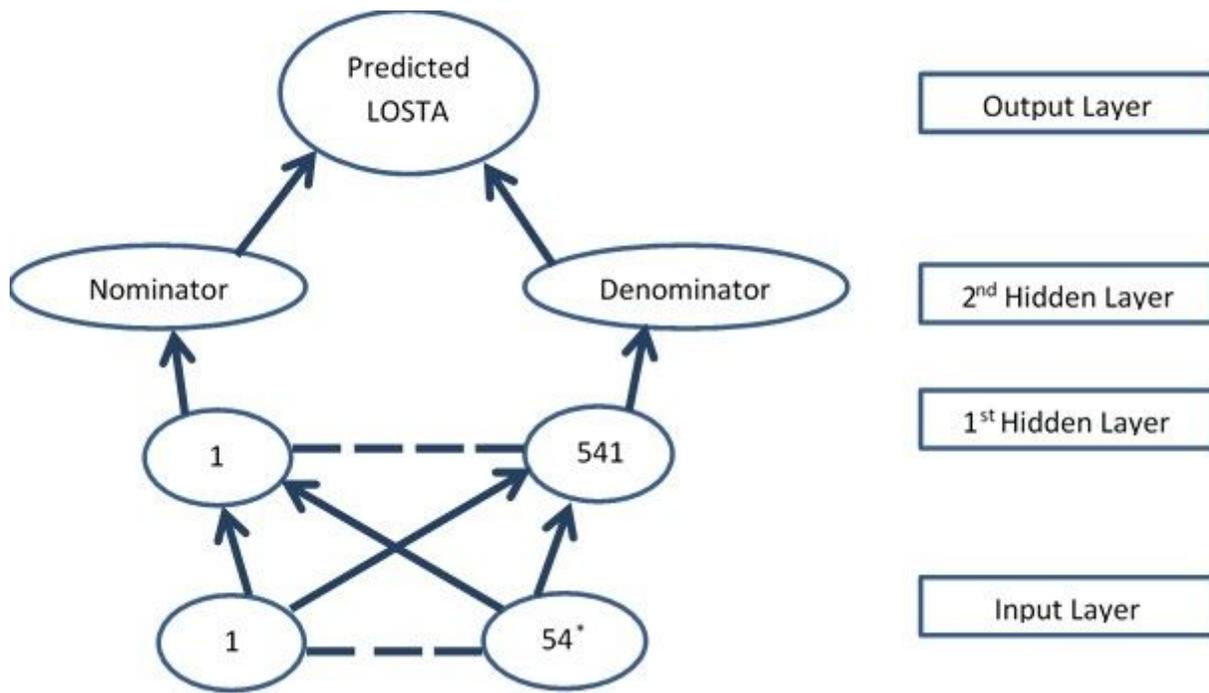


Figure 2

Artificial Neural Network Model Structure for the Length of Hospital Stay after the Index intervention.
 Endnote: *number of input nodes varied as we included the significant predictors or mismatched variables predicting the outcome

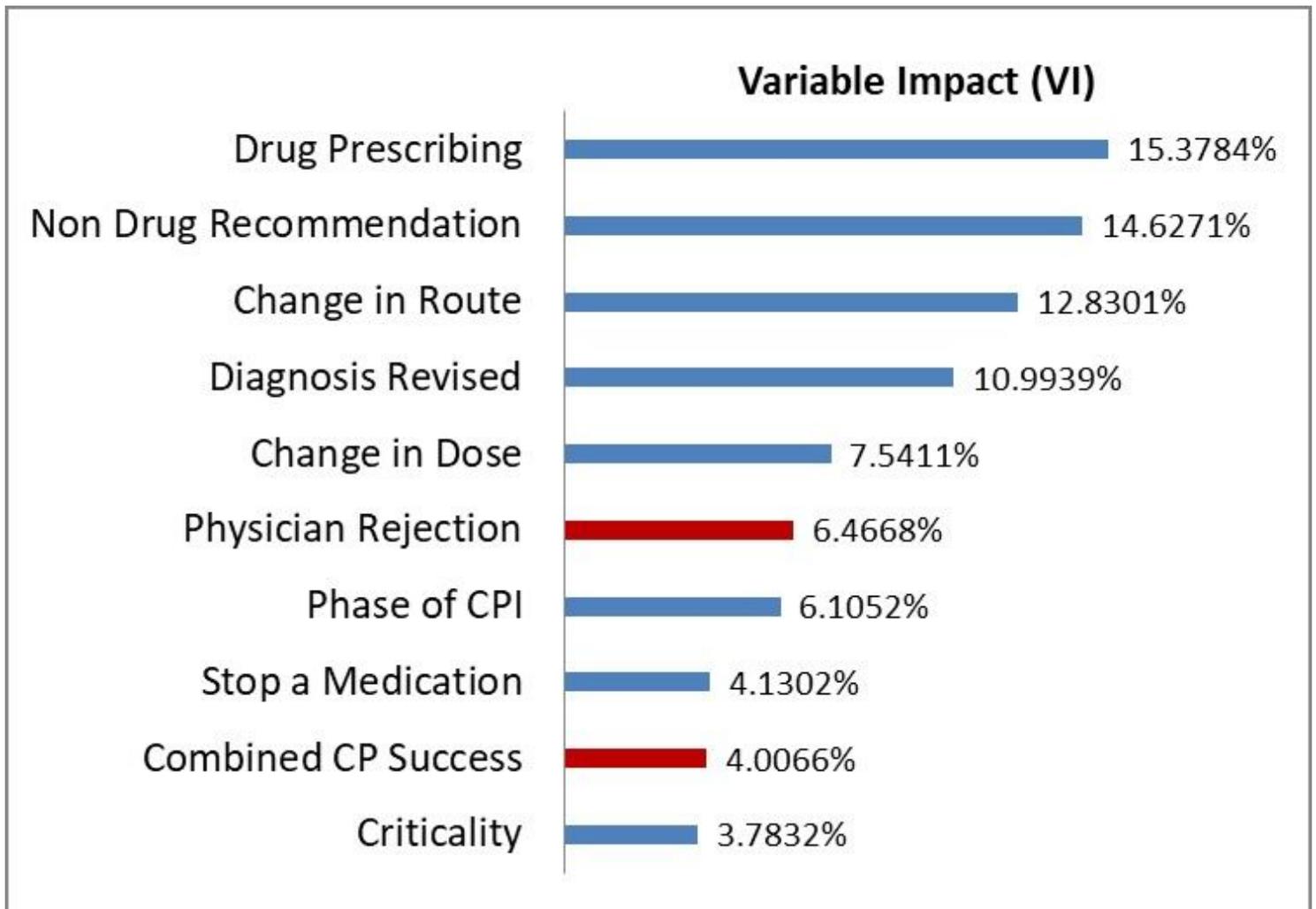


Figure 3

Variable Impact for Length of Hospital Stay after the Index Intervention Artificial Neural Network, all 54 input variables included.

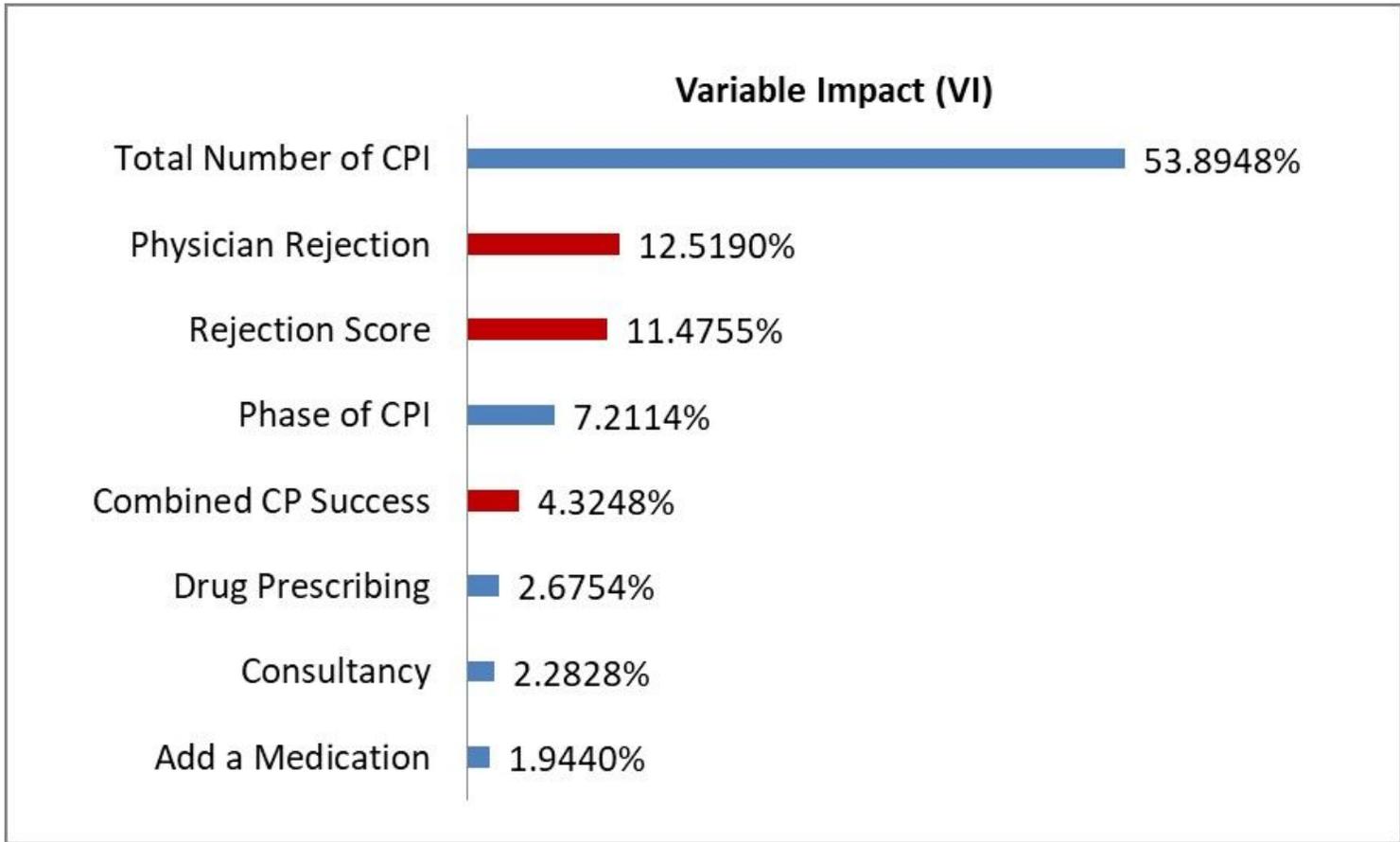


Figure 4

Variable Impact for Length of Hospital Stay after the index intervention, only mismatched 19 input variables included.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.JPG](#)
- [Table2.JPG](#)