ABSTRACT

In a data-scarce field such as healthcare, where models often deliver predictions on patients with rare conditions, the ability to measure the uncertainty of a model’s prediction could potentially lead to improved effectiveness of decision support tools and increased user trust.

This work advances the understanding of uncertainty estimation for classification and risk prediction on medical tabular data, in a three-fold way. First, we analyze two families of promising methods and discuss the preferred approach for uncertainty estimation for classification and risk prediction. Second, these remarks are enriched by considerations of the interplay of uncertainty estimation with class imbalance, post-modeling calibration and other modeling procedures. Finally, we expand and refine the set of heuristics to select an uncertainty estimation technique, introducing tests for clinically-relevant scenarios such as generalization to uncommon pathologies, changes in clinical protocol and simulations of corrupted data. These findings are supported by an array of experiments on toy and real-world data.

1 Introduction

Risk prediction models are among the most common prognostic models in healthcare research: a staggering amount of risk models has been developed in different subfields of medicine, to predict the probability of adverse events ranging from in-hospital mortality to post-surgical incontinence. The reason for this proliferation is that an accurate risk assessment can aid decision making and potentially lead to great improvements in patient outcomes [Jaspers et al., 2011]. To date, risk prediction models are incorporated in numerous clinical protocols and form the basis of several guidelines (see e.g. Mosca et al. [2011]). There is however a potential issue that is often not addressed in the development of said models, namely that the risk score, already reflecting uncertainty about the outcome, does not necessarily capture the uncertainty due to lack of data. This problem is particularly felt in medical applications, where the size of data sets is often limited: models with good overall performance are nonetheless likely to give unreliable prediction on uncommon patients. Indicating the level of confidence in a prediction, or outright discarding the predictions that are too uncertain, could vastly improve the effectiveness of decision support tools as well as increase the trust of users in models’ suggestions.

A growing body of literature in the field of Machine Learning is concerned with the development of techniques to estimate the uncertainty of individual predictions. These efforts were mostly directed towards regression tasks, with less attention devoted to classification and risk prediction. Moreover, among the few medical applications, most of them focused on image data. To enable the use of uncertainty estimation techniques for a wider range of prognostic and diagnostic models, what is required is a systematic array of experiments demonstrating which techniques work in practice for classification and risk prediction on tabular data, the format in which the vast majority of medical data is stored.

As an example, Damen et al. [2016] report that until 2013 at least 363 prediction models had been developed for the specific task of predicting the cardiovascular disease risk in the general population.
The goal of this paper is to fill this gap and provide practical insights that can be used in the development of medical AI. To this end, we evaluate the benefits and limitations of two different but intuitive frameworks to incorporate uncertainty in a risk prediction model in healthcare, running several experiments on toy and real-world tabular data. For the latter, we focus on the task of mortality prediction in the Intensive Care (IC).

To summarize our contributions:

1. for the tasks of classification and risk prediction, we analyze two families of promising methods; we conclude that ensembling methods could be valuable for a classification task, whereas methods for the detection of novel or rare examples are preferable in the case of risk prediction;
2. we analyze the interaction of uncertainty estimation with other common modeling procedures such as class weighting and post-modeling calibration;
3. we expand and refine existing heuristics to decide if and how to employ an uncertainty estimation technique; for detection of out-of-domain examples we address multiple clinically-relevant scenarios such as generalization to different ethnic subgroups and uncommon pathologies, as well as simulation of corrupted data.

2 Related Work

Uncertainty is often divided into two types: aleatory uncertainty and epistemic uncertainty. The former refers to the intrinsic randomness of a phenomenon, whereas the latter is presumed to be caused by lack of knowledge [Der Kiureghian and Ditlevsen, 2009].

Aleatory uncertainty In Machine Learning (ML henceforth) literature, aleatory uncertainty is interpreted as uncertainty due to ambiguity or noise in the data. In a classification problem this translates to having inherently overlapping classes. Therefore, such uncertainty cannot be resolved by observing more data points from the same source, but only by adding extra features, improving the quality of existing features, or other operations that could possibly make the classes separable. In medical prognostic models we almost always face a certain degree of aleatory uncertainty, as we do not have perfect information to predict future events.

Epistemic uncertainty On the other hand, epistemic uncertainty can be interpreted as uncertainty due to a lack of knowledge about the optimal predictor. This can be divided into uncertainty over model parameters and uncertainty over model structure (or hypothesis class). Epistemic uncertainty can be resolved by observing more data, and is therefore also known as reducible uncertainty [Urbina and Mahadevan, 2011]. In Figure 1 we illustrate the difference between uncertainty due to inherent overlap of the classes, and uncertainty due to lack of knowledge about the optimal predictor.

Modeling uncertainty There has been much work on modeling aleatory uncertainty in a classification problem, as this is what standard probabilistic classifiers are targeting by modeling the probabilities \( p(y|x) \). However, these probabilities often result in unjustified high confidence for points far away from the training data and thus fail to represent epistemic uncertainty [Gal and Ghahramani, 2016]. An intuitive way to better capture epistemic uncertainty is by modeling uncertainty over possible models or model parameters, which we will refer to as parameter uncertainty. This builds on the idea that plausible models, which we can conceptualize as different ‘experts’, will have different opinions about points far away from the training data. One can model uncertainty over model parameters by learning a posterior distribution over said parameters by (approximate) Bayesian modeling [Gal and Ghahramani, 2016; Hüllermeier and Waegeman, 2019]. Applications in healthcare, e.g. Filos et al. [2019a], Leibig et al. [2017], showed that we can benefit from Bayesian deep learning techniques to incorporate epistemic uncertainty for detecting diabetic retinopathy from fundus photos, while Ruhe et al. [2019] examined their application to mortality prediction in Intensive Care. However, other approaches such as linearly combining predictions into ensembles, have also shown to work well at capturing epistemic uncertainty [Fumera and Roli, 2004; Osband et al., 2016] and are able to outperform Bayesian methods [Lakshminarayanan et al., 2017].

Another straightforward way to estimate epistemic uncertainty is by simply using a separate model to give an indication of novelty or rarity, for example unconditional density estimation [Bishop, 1994; Markou and Singh, 2003]. We will refer to this type of uncertainty as novelty detection. This paradigm relies on the idea that model’s predictions are likely to be less reliable in low density areas, since the model has no ‘experience’ with similar data. Additionally, other lines of research model aleatory and epistemic uncertainty with fuzzy preference modeling [Senge et al., 2014].

2 In ML literature it often happens that only uncertainty over model parameters is considered and referred to as epistemic uncertainty.
Uncertainty estimation for classification and risk prediction in medical settings

possibility theory and evidence theory [Hüllermeier and Waegeman, 2019]. Other methods involve retraining a model with new data and comparing the difference between the trained and retrained model [Kukar and Kononenko, 2002]. Finally, there are methods leveraging the disagreement of a classifier with another model such as a generative model or a nearest neighbour classifier [Myers et al., 2020; Jiang et al., 2018].

With this plethora of advanced techniques, it is daunting for practitioners to even decide what method to implement. We decided to focus on two techniques that are most intuitive (let us not forget that uncertainty must eventually be interpretable for clinicians), allow us to work with any powerful discriminative model, do not require using training data during prediction, and require little effort to incorporate in a modeling process. We will investigate ensembles of probabilistic classifiers as representatives of parameter uncertainty. These methods have been shown to be at least on par with Bayesian techniques in terms of performance [Filos et al., 2019b; Lakshminarayanan et al., 2017] and are intuitive and straightforward to implement. Furthermore, there is the advantage that ensembling can be used in combination with any probabilistic classifier. We implement a variational autoencoder as a representative of a novelty detection method [Kingma and Welling, 2014].

3 Methods

We first introduce the models and subsequently the techniques used to evaluate them.

3.1 Models

3.1.1 Deep ensemble

We implemented an ensemble of 5 simple, multi-layer perceptrons with two hidden layers of 100 neurons. They were all independently randomly initialized and trained on the same data, but with data points presented in a randomly shuffled order. For further specifications we refer to Appendix B.

3.1.2 Bootstrapped Logistic Regression

The widely used method called ‘bootstrap’ was introduced already in Efron [1979]. It mimics repeated sampling from the true data distribution by resampling with replacement from the data set. For our present purpose, we created an ensemble by training multiple models on bootstrapped samples of the data set. We used this method as an intuitive simple counterpart to the deep ensemble, in order to investigate the influence and added value of model flexibility. We again opted for an ensemble of 5 models, training each model on a different bootstrapped sample of the data of the same size as the training data. Again, we refer to Appendix B for implementation details.

For both ensemble models the prediction was calculated as the average over the predictions of the individual
ensemble members. Uncertainty was calculated as the entropy of a prediction. This is an intuitive uncertainty estimate: it is highest when the predicted probability is 0.5 and lowest when the probability is either 0 or 1.

3.1.3 Variational Autoencoder

For obtaining an indication of novelty we trained a variational autoencoder (VAE) \cite{Kingma2014}. We picked this model because it is suitable for high-dimensional data and widely applicable to different data types. A VAE can be understood as a pair of neural networks, an encoder and a decoder. An encoder network maps an input to a lower dimensional latent distribution, while a decoder network attempts to convert this lower dimensional representation back to the original input. We use the VAE’s reconstruction error as a measure of uncertainty, following the intuition that the autoencoder will only learn to reconstruct data that is similar to the data it has seen before. Once more, we refer to Appendix B for further implementation details.

3.2 Evaluation methods

3.2.1 Metrics

Alongside the area under ROC curve (abbreviated with AUC-ROC) to measure performance, we used the Expected Calibration Error (ECE) metric \cite{Naeini2015} to evaluate the calibration of our models. ECE is calculated as follows:

\[
ECE = \frac{1}{N} \sum_{k=1}^{K} N_k |\bar{y}_k - \bar{o}_k|
\]

where $K$ is the number of mutually exclusive equally-sized bins, $\bar{y}_k$ is the mean predicted probability within bin $k$ and $\bar{o}_k$ the observed outcome probability (fraction of positives) within $k$. In our implementation we employed 10 bins, so the first bin included all data points with a predicted probability between 0 and 10\%, the second bin between 10\% and 20\%, and so on.

An uncertainty estimate is useful if the model can be trusted when it is confident, and can be ignored when it is uncertain. Whether this is the case can be evaluated by sorting the predictions by their estimated uncertainty and tracking the performance metrics as larger and larger portions of uncertain data points are excluded, simulating what would happen to performance if we were to remove uncertain data points.

3.2.2 Out Of Domain detection

It is likely that a model will not give reliable predictions for patients that are not well represented in the training data. Therefore, a good uncertainty estimate should be higher for these patients. Out Of Domain (OOD) detection is often evaluated in computer vision, where one can simply feed a picture from another domain to a classifier and check whether the model is indeed uncertain. Alas, when dealing with tabular data this is not as straightforward. We devised a number of scenarios to simulate clinically-relevant situations and evaluated the uncertainty estimate empirically. The evaluation was performed by excluding a specific group of patients from the training data and then testing the model on this excluded group as well as on a normal test set without patients from this group. We expect the uncertainties to be higher on this OOD group as compared to the normal test set, which consists of patients similar to the training data. To quantitatively evaluate the ability of detecting these OOD groups based on uncertainty, we followed Hendrycks and Gimpel \cite{Hendrycks2017}: all predictions, both from the normal test set and the OOD group, were ranked according to estimated uncertainty. Thresholds were used to predict which samples are OOD and AUC-ROC was calculated for the varying threshold. As a consequence, AUC-ROC is highest if all OOD patients have higher uncertainty than all patients in the regular test set. We experimented on the following scenarios:

- **Rare or new disease** One possibility is that a clinic or a ward starts receiving patients with an illness not previously treated in that structure, either because of a new pathology or because of a change in protocol. We simulate this by using ICD-9 diagnoses that are given at the end of each hospital stay, labeling as OOD all patients with a specific pathology.

- **Generalization to other ethnic groups and genders** We could imagine that a certain population group, such as an ethnic minority or gender, is not represented in the training data. In this context we would also want a higher uncertainty for such OOD patients to avoid unwarranted generalizations.

\[3\text{See Appendix A for the descriptives of the various groups.}\]
Uncertainty estimation for classification and risk prediction in medical settings

Different admission type Another scenario could be a change in hospital organisation leading to a different patient distribution. For example, a new procedure could get instated where a specific type of patients (e.g. a specific type of surgery) now gets referred to the Intensive Care, whereas previously they were referred to another ward. We simulate this situation by considering as OOD either the emergency/urgent patients (unplanned medical care), or the elective patients (planned hospital admission).

Corrupted data Another OOD group consists of patients with abnormal feature values, for example, arising as a consequence of faulty sensors, software bugs or human typing errors. To simulate this mishaps we construct a perturbed version of the test set by picking a random feature and re-scaling it across the test set. The desired outcome is higher uncertainties for the perturbed test set compared to the regular test set. We repeat the same procedure for 30 randomly selected features, as different features might have different effects, and then average the results. This perturbation experiment is repeated twice with a multiplication factor of 10 and 1000.

4 Cohort

We performed experiments on the MIMIC-III data set [Johnson et al., 2016], which comprises health data from IC unit admissions from the Beth Israel Deaconess Medical Center in Boston, Massachusetts. MIMIC-III is well-documented and represented in literature with benchmarks for comparison [Purushotham et al., 2017, Harutyunyan et al., 2019]. We used the same data extraction pipeline as Harutyunyan et al. [2019], who specified multiple benchmark tasks. We focused only on risk prediction of in-hospital mortality based on the first 48 hours of data. From the 46476 patients and 61532 IC stays in the MIMIC-III data set, data points are selected based on patient age (≥ 18 years) and length of stay (≥ 48 hours). Furthermore, stays were excluded when there was no data in the first 48 hours or when there were multiple IC transfers within one hospital admission. After selection, the cohort consisted of 21139 IC stays corresponding to 18094 patients, with a mortality rate of 13.23%. We employed the feature engineering for the Logistic Regression model in Harutyunyan et al. [2019], where for 17 selected clinical variables, six statistics are calculated on seven sub-sequences of a time series. The sub-sequences consist of the full time series, the first 10% and last 10%, the first and last 25%, and the first and last 50%. The statistics are minimum, maximum, mean, standard deviation, skew and the number of measurements, which are all standard-scaled. This results in 714 features in total. We also adopted the same train, test and validation split, of size 14681, 3236, 3222 respectively. Additionally, we used toy data to highlight key intuitions. For a description of the toy data generation process we refer to Appendix C.

5 Results

The desired properties of an uncertainty estimate differ depending on the use case of the model. We consider two use cases - classification and risk prediction.

5.1 Classification

In a classification setting, we are interested in predicting hard labels with confidence. The clearest role of uncertainty is to abstain from giving predictions for patients for which the label is uncertain. Therefore, the most important property of an uncertainty estimate in this setting would be improved discrimination (measured by AUC-ROC) when excluding uncertain predictions. Furthermore, a high uncertainty on OOD patient groups is desirable. Finally, a secondary requirement would be that the predictions are well-calibrated. This is not necessary for the classification task, but could be useful if we are to interpret the risk predictions as probabilities to set a threshold.

5.1.1 Toy data

We begin by showing what the different methods capture on toy data. The red and blue points denote data points from two different classes. In Figures 2 and 3, we observe the difference between using a single model and an average over ensemble members: the ensembles produce a wider decision boundary further away from the data, reflecting the diverging beliefs of different single models. In Figures 2c and 3c, we show how the predicted probabilities translate to uncertainty, defined by the entropy. On toy data, we can observe that the NN and LR ensembles capture similar uncertainties, but this will be different in a situation where classes are not linearly separable. Moreover, especially with less data available, the NNs might (over-)fit the data in many different ways, whereas LR models have less flexibility. This will result in wider, more density-like uncertainty for the deep ensemble.

In Figure 4, we see an example of what might happen in an unbalanced setting. The model focuses most on learning to predict the majority class with high certainty. As a consequence, when using entropy to reject examples based on
Uncertainty estimation for classification and risk prediction in medical settings

Figure 2: Showing the predicted probabilities of a single LR model (a), the average of the predicted probabilities of bootstrapped LR models (b) and the entropy of these predicted probabilities (c).

Figure 3: Showing the predicted probabilities of a single neural network model (a), the average of the predicted probabilities of differently initialized neural networks (b) and the entropy of these predicted probabilities (c).

Figure 4c showcases that, in an imbalanced problem, the minority points might lie in a relatively low-density area of the space.

5.1.2 Confidence-performance plots on MIMIC-III

We turn to the experiments on real-world data, for the prediction of mortality in IC. We show the confidence-performance plots with and without using class weighting. We employ entropy of the prediction as the uncertainty estimate, both for the single model and the ensemble model (where entropy of the average prediction is taken). We use the VAE uncertainties together with the predictions of the best single model, in this case the NN.

Without class weighting Figure 5a shows AUC-ROC against the fraction of included test data points, where the most certain points are included first. We observe that for all methods AUC-ROC worsens when excluding uncertain points. This is counter-intuitive but can be explained by class imbalance: since the classes are unbalanced, the model put most focus on learning to predict the majority class (in this case the negative class) with high certainty, like in Figure 4a. The fact that the most certain points are points from the majority class, can be seen in Figure 5b, where the fraction of

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4The exact implementation of class weighting is described in Appendix B.
positive examples in the confident subset is shown. In Figure 5c we observe that the calibration error is very low in all subsets, and seems to be smaller for the most certain data points. This is desirable, but the differences are so small that it is hard to say whether they are true effects or artifacts of binning.

With class weighting When using class weighting, the models artificially devote more attention to the minority class. We see this back in Figure 6b: the most confident data points do not only originate from the majority class but are relatively balanced. We also observe in Figure 6a that AUC-ROC now improves when excluding the most uncertain data points. For both LR and the NN, the ensemble versions have a similar AUC on all data as compared to the single models. However, the uncertainty estimates of the ensemble models seem to be better calibrated as they lead to more improvement in AUC-ROC when excluding uncertain data points. This suggests that the ensemble methods capture some measure of epistemic uncertainty on top of the aleatory uncertainty captured by the single models. Nevertheless, when looking from a practical point of view, it is unlikely that we would want to use uncertainty to exclude more than 20% of the data. Keeping this in mind, we see that the difference in AUC-ROC between the ensemble methods and the single methods is relatively small when excluding only 20%. This means that it might be a reasonable choice to use the baseline uncertainty in practice: especially the single NN has well-calibrated uncertainty estimates.

Finally, class weighting causes the risk predictions to be poorly calibrated. Therefore, to be interpreted as true risk, predictions need to be corrected. An easy and effective way to re-calibrate predictions is by Platt scaling via a held-out
Uncertainty estimation for classification and risk prediction in medical settings

Figure 6: Confidence-performance plots when using class weighting. Showing mean and standard deviation over 5 random seeds.

We see in Figure 6c that after this additional step, we can still obtain a good calibration on the different confident subsets of the data, with an expected calibration error of around 0.02.

5.1.3 OOD experiment

Detection of OOD In Figure 7, we see the AUC-ROC scores of OOD detection using the uncertainty of the different class-weighted ensemble methods compared to the VAE. We observe that using the reconstruction error of the VAE, each OOD group is detected with an AUC-ROC higher than 0.5, indicating that the characteristics of the OOD patients are indeed (at least slightly) different from the training data. On the contrary, bootstrapped LR and NN ensemble do not seem to detect the OOD groups effectively. The group that is most clearly detected is the group of emergency admissions, while the group of elective admissions is not recognized as OOD and receives a lower uncertainty than the test set. The other groups all have an AUC-ROC close to 0.5, meaning the uncertainties are equally high for the OOD group compared to the test set.

Figure 7: OOD detection and AUC-ROC of the model on the corresponding subgroup.
**Subgroup AUC-ROC**  As an additional check, we contrast OOD detection with generalization to unseen subgroups. We train a model on all data except the selected OOD patients, and evaluate the trained model on these OOD patients. This gives an idea of how well the model can generalize to this unseen group: if the model generalizes well, then arguably it does not matter if the predictions are overly confident; if on the other hand the model does not generalize well, we would want to be warned for this by high uncertainty. In general, we see in Figure 7 that this seems to be the case. Consider the model that had not seen any emergency admission in the training data, on the first line. This model does not generalize very well to emergency admissions (with a relatively low AUC-ROC), but the same group also receives higher uncertainty estimates, so the model seems to know what it does not know. For the group of elective admissions we see an opposite phenomenon: the predictions are relatively confident even though the model has not seen elective admissions. However, the performance on this subgroup is still very high. This pattern seems to repeat in most subgroups, where better OOD detection (higher uncertainty) relates to worse subgroup performance and low uncertainty relates to better performance.

To conclude, ensemble models do not generally give higher uncertainty to patient groups that are different from the training data, contrary to the VAE. However, ensembles seem to give higher uncertainty to groups on which the classification ability does not generalize well, which is likely the most important aspect.

5.1.4 Corrupted data as OOD

We observe in Figure 8 that on real data the VAE gives on average higher uncertainty to corrupted data compared to regular test data, whereas the other models do not. Instead, ensemble models get on average more certain when rescaling a random feature.

![Figure 8: The mean and standard deviation of the detection AUC-ROC over 30 different randomly re-scaled features, for three different scaling factors.](image)

This behaviour is explained by the experiments on toy data in Figure 9, we see that even if we zoom very far from the training data, as we simulate in the corrupted data scenario, the ensemble model can still be very confident in remote areas. Even giving the model more flexibility or decreasing the data set size did not change the fact that there are always confident areas far away from the training data.

In light of the task at hand, this behaviour could be reasonable. For example, consider a situation where a model learns a linear relation between body temperature and risk. Even though a body temperature of $100 \text{ } ^\circ C$ does not exist, it is reasonable for the model to think that the patient has an extremely high risk. This underlines a tendency to generalize that is both a limitation and a strength of the task-specific uncertainty methods.

5.2 Risk prediction

So far, we looked from the perspective of using the risk model for a classification task. However, often risk estimates are used directly to assist non-binary decisions or to stratify patients into groups (e.g. high, medium or low risk) for which different actions hold. Clearly an optimal model still discriminates perfectly, but in this approach we want to accept uncertain predictions if they are the best we can get given the data: aleatory uncertainty is something we choose...
Uncertainty estimation for classification and risk prediction in medical settings

Figure 9: ‘Zooming’ out, showing the entropy of a Logistic Regression ensemble (a), a NN ensemble (b), and the estimated negative log-likelihood (c) on the toy data.

In this setting, the quality of the risk predictions is what we care about most. The calibration error gives a global idea of quality of probabilistic predictions. If we would observe that the calibration error decreases when excluding uncertain predictions, this would indicate that uncertainty relates to prediction quality. Alas, local mistakes can be evened out by binning, which makes it hard to evaluate the influence of uncertainty on prediction quality with the calibration error. Again, an improved AUC-ROC could indicate improved ranking and therefore that the uncertain predictions were less reliable. However, the quality of a risk prediction is not necessarily related to good discrimination. For example, if most data points are in areas with inherent overlap, the model will likely give most reliable risk predictions to this area with high aleatory uncertainty. It is important that the AUC-ROC stays reasonably high when excluding uncertain predictions, as otherwise the model would not be useful, but it does not necessarily need to improve.

Calibration We observed in Figures 5c and 6c that the calibration error improves when excluding uncertain predictions based on the uncertainty given by the ensembling methods, and that the calibration error is always slightly lower when using ensembling as compared to using a single model. However, we have seen that the calibration error on the total group of patients is already low or the predictions can easily be calibrated to result in a low calibration error. As the differences between calibration on the different confident subgroups are small, and the calibration metric is inherently imperfect because of binning artifacts, we cannot draw relevant conclusions about the relation between uncertainty and the quality of predictions.

Detection of OOD We noticed in Figures 7 and 8 that the VAE was the only method that can detect data that differs from the training data reasonably well.

AUC-ROC We observed in Figure 6 that excluding uncertain predictions based on the VAE uncertainty results in a slightly lower AUC-ROC. AUC-ROC likely decreases because some of the most obvious positive cases are in a low density area, e.g. the extremely sick. We see this in Figure 5b, where the percentage of positive points is lower for the most confident subsets of the data. In practice, this might not be a problem in a decision support setting, as obvious cases would also be simple for clinicians to handle without the help of a prediction. In this context, an indication of dissimilarity from previously seen cases could already be informative enough.

6 Discussion

In light of our findings, we draw some conclusions on the best usage of the aforementioned uncertainty techniques in medical applications.
6.1 Classification

**Best method** We would argue that ensembles of probabilistic classifiers are most suitable for a situation where the goal is to perform automatic classification with a reject option.

We have observed that by excluding predictions based on the confidence score of a probabilistic classifier, discrimination can significantly be improved. Using an ensemble of probabilistic classifiers has an even larger positive influence on AUC-ROC, for the NN ensemble but even for the simple LR ensemble. It is worth remarking that this added value will be different dependent on data set size, model type and complexity of the data set. In some situations it might be worth the extra complexity and reduced interpretability, whereas in other cases it might not be necessary.

**Limitations** Although ensembling methods result in larger improvement of AUC-ROC, these methods do not necessarily give higher uncertainty to OOD groups and could even be more confident about such data. The simulation of corrupted data taught us that we cannot expect to get high uncertainty estimates on data with abnormal feature values. This might not be a problem, as we could arguably deal with those cases in a preprocessing stage. It is however important to keep in mind that the model might still be overconfident about its own generalizability, even when using ensembling methods. Another difficulty about this approach is that the quality of an uncertainty estimate is sensitive to modeling assumptions of the ensemble members like the model architecture, as well as parameters specific to the ensemble such as the bootstrap size.

6.2 Risk prediction

**Best method** When the goal is to use risk predictions directly to inform decision-making, a more conservative approach like novelty estimation is the safest option.

We noted that by excluding predictions based on an estimate of novelty, we can successfully give higher uncertainty to OOD patients and corrupted data. With this technique we might underestimate the ability of the model to generalize, but we can trust to be informed about patients for which the model has no experience. We also showed that excluding data points based on novelty might hurt discrimination, likely because obviously positive or negative points lie in a low-density area. This is something to be aware of, but in a decision support setting, the slightly worsened discrimination might not be a problem as the low-density obvious cases (e.g. the extremely ill) will likely already be easily classifiable by the clinicians.

**Limitations** A limitation of having a separate novelty detection component is that we get an extra, possibly ‘black box’ model that needs to be explained to the user. Furthermore, novelty detection is not a trivial task on its own. Finally, another impediment when using this type of uncertainty to detect unreliable risk predictions is that it is hard to estimate or quantify the added value of the uncertainty estimate. This could however be measured empirically via a real-world trial, relating the use of uncertainty to patient outcomes and user trust.

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A  OOD descriptives

Table 1: Characteristics and origin of the selected subgroups.

| Count Mortality rate (%) | MIMIC table | Field                          |
|---------------------------|--------------|--------------------------------|
| Emergency/Urgent admissions 18299 14.8 | ADMISSIONS | ADMISSION_TYPE                |
| Elective admissions 2840 3.4 | ADMISSIONS | ADMISSION_TYPE                |
| Ethnicity: Asian 492 13.8 | ADMISSIONS | ETHNICITY                      |
| Ethnicity: Black/African American 2016 9.2 | ADMISSIONS | ETHNICITY                      |
| Ethnicity: Hispanic/Latino 679 8.1 | ADMISSIONS | ETHNICITY                      |
| Ethnicity: White 15043 12.9 | ADMISSIONS | ETHNICITY                      |
| Female 9510 13.5 | ADMISSIONS | GENDER                         |
| Male 11629 13 | ADMISSIONS | GENDER                         |
| Thyroid disorders 1729 13.5 | DIAGNOSES_ICD | ICD9_CODE       |
| Acute and unspecified renal failure 4275 21.7 | DIAGNOSES_ICD | ICD9_CODE       |
| Pancreatic disorders (not diabetes) 319 14.1 | DIAGNOSES_ICD | ICD9_CODE       |
| Epilepsy, convulsions 965 15.3 | DIAGNOSES_ICD | ICD9_CODE       |
| Hypertension with complications 2274 15.1 | DIAGNOSES_ICD | ICD9_CODE       |

B  Model specifications

**NN ensemble**  For the experiments on the MIMIC data we create an ensemble of 5 neural networks with two hidden layers of 100 neurons, ReLU activations, a dropout rate of 0.5 and a sigmoid activation in the final layer. The NNs were all independently trained with the Adam optimizer, using default learning rate $1e^{-3}$, cross-entropy loss and a batch size of 256. We implemented early stopping and quit training when the validation loss did not improve for 2 epochs. For the experiments on toy data we employed smaller networks with one hidden layer of 5 neurons, training with a smaller batch size of 8 and for 20 epochs. We implemented class weighting based on the relative class frequencies in each mini-batch. We calculated the positive weight for each batch $b$ as $w_b^+ = \frac{N_b}{N_b^+}$, that is, the number of negative examples divided by the number of positive examples in the mini-batch. This results in the following weighed loss $L_b$ for the mini-batch:

$$L_b = -\frac{1}{N_b} \sum_{i=1}^{N_b} \left[ w_b^+ \cdot y_i \log \hat{y}_i + (1 - y_i) \log(1 - \hat{y}_i) \right]$$

where $N_b$ is the number of data points in the batch, $y_i$ the true label and $\hat{y}_i$ the predicted probability. We implemented the NN ensemble in PyTorch.

**Bootstrapped Logistic Regression**  We train an ensemble of 5 models, training each model on a different bootstrapped sample of the data of the same size as the training data. We used the scikit-learn implementation of Logistic Regression [Pedregosa et al. 2011] with the L-BFGS-B solver. We set the regularization coefficient to $C = 1e^{-2}$ on real data and to 0 on toy data. For class weighting we used the same weighting as described for the Deep Ensemble, but we employed a constant positive weight based on all data instead of one that is batch-dependent.

**Variational Autoencoder**  We implemented the VAE in PyTorch. The latent distribution was modeled as a 500-dimensional normal distribution with diagonal covariance. The output distribution of the decoder was also modeled as a normal distribution with diagonal covariance. We trained the model with Adam optimizer, again using a default learning rate of $1e^{-3}$. The batch size was set to 256 and training lasted 30 epochs. The encoder and decoder both had no hidden layer, as adding hidden layers made training very unstable and did not seem to improve performance significantly. During test time, we took 10 samples from the latent distribution and calculated the average reconstruction error over these sample. This reconstruction error is what we use as a measure of uncertainty.

C  Toy data generation

For the balanced data examples, we generated two equally-sized clusters, one for each label, both from a multivariate normal distribution. The means of the positive and negative clusters were $(2, 2)$ and $(-1, -1)$ respectively. Both
clusters had diagonal covariance matrices defined as 4 times the identity matrix. For the unbalanced data set, we used the same multivariate normal distribution for the negative cluster, and for the positive cluster the same mean $(2, 2)$ with a covariance of 2 times the identity matrix. We generated 6 times as many points in the negative cluster as compared to the positive cluster. In both cases we generated 200 points for training.